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Review

Opportunities for Cellular Rejuvenation in Alzheimer's Disease: How Epigenetic Reprogramming and Chaperone-Mediated Autophagy Are Enabling Next Generation Therapeutic Approaches

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Abstract

Age remains the largest risk factor in the development of neurodegenerative diseases such as Alzheimer's disease (AD). Numerous cellular hallmarks of aging contribute to the advancement of the pathologies associated with neurodegenerative disease. Not all cellular hallmarks of aging are independent and several fall into the broader category of cellular rejuvenation, which captures returning cells to a more youthful, improved functional state. Cellular rejuvenation is quickly becoming a hot topic in the development of novel therapeutic modalities for a range of diseases. Therapeutic approaches utilizing cellular rejuvenation technologies are rapidly advancing and will represent the next phase of AD therapeutics. This review focuses on two important processes, epigenetic reprogramming, and chaperone-mediated autophagy (CMA) that play a critical role in aging and in neurodegenerative diseases and the potential therapeutic approaches (gene therapy, small molecule) towards targeting these mechanisms. In aging and in AD, epigenetic changes on DNA (e.g., hypermethylation on CpG islands) lead to alterations in gene expression. Partial epigenetic reprogramming utilizes transcription factors to remove the epigenetic marks and to rejuvenate cells to a more youthful state. During aging and in neurodegenerative disorders, CMA becomes impaired resulting in a buildup of proteins known to be associated with neurodegenerative pathologies. The protein buildups lead to aggregates that preclude proteostasis leading to cell toxicity. Small-molecule CMA activators restore proteostasis and limit toxicity enabling cellular rejuvenation.

Key words: Epigenetic reprogramming, chaperone-mediated autophagy, cellular rejuvenation, OSK, LAMP2A.

Introduction

The greatest known risk factor for developing Alzheimer's disease (AD) is aging (1). With an aging baby boomer population, the number of people over age 65 with mild to moderate AD is expected to more than double from 6.7 million in 2023 to 13.85 million in 2060 (2). Alzheimer's disease is a progressive neurodegenerative disease with pathology that begins long before clinical cognitive symptoms emerge. There are multiple stages of AD starting with the preclinical phase where amyloid and tau pathologies are developing and hippocampal overactivity is beginning, but clinical cognitive symptoms have not yet emerged (3, 4). The next phase (prodromal AD or mild cognitive impairment due to AD (MCI)) includes the earliest cognitive impairments predominantly related to changes in episodic memory (5). During this phase the hippocampus activity ramps up and tau pathology continues to worsen (4–9). As the disease continues to progress, the clinical cognitive domains as well as functional domains become increasingly impaired leading from mild to moderate to severe dementia (10). Like the projected trend for AD, the number of people over age 65 with MCI is expected to grow from 13.5 million in 2023 to 21.6 million in 2060 (2). Taken together, the increasing numbers of potential patients who will experience a progressive neurodegenerative disease in the coming decades has the potential to lead to a tremendous burden for caregivers and on the healthcare system.

Despite the advancements in understanding and earlier diagnosis of neurodegenerative diseases, the current treatment landscape for AD is limited. Available treatment options include the symptomatic treatments (acetylcholinesterase inhibitors, memantine) and the more recent introduction of amyloid antibodies such as Aduhelm (aducanamab) and Leqembi (lecanamab), which markedly reduce the number of amyloid plaques and have some clinical benefit as measured by the clinical dementia rating scale sum of boxes (CDR-SB) (11, 12). While the amyloid antibodies represent a modest clinical advance, they have some concerning safety limitations due to the risk of brain microhemorrhages which require extensive monitoring by magnetic resonance imaging (MRI) (11, 12).

Novel approaches to the treatment of AD and other neurodegenerative disorders are needed to address the unmet medical need to slow, delay or even reverse AD clinical symptoms and pathology. This unmet need was highlighted by Lopez-Otin et al, who used the aging landscape as a focus to describe numerous cellular processes or hallmarks of aging, that become impaired. These hallmarks include genomic instability,

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telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication (13). More recently, autophagy, microbiome disturbance, altered mechanical properties, splicing dysregulation, and inflammation have been added to the growing list of impaired processes in aging (14, 15) with targets for some of these already making their way into clinical trials (16). Cellular rejuvenation technologies, such as stem cell therapies, gene editing (eg siRNA, CRISPER-Cas9), and other regenerative medicine approaches (neurotrophic and growth factors immunotherapies), have shown promising potential in various areas of research and treatment, including Alzheimer's disease (AD). Cellular rejuvenation involves returning aged or injured cells to a more youthful state thereby restoring normal cellular function to reverse the effects of diseases of aging such as AD (17). This review will address how epigenetic reprogramming and CMA play a critical role in aging and in neurodegenerative diseases. It will discuss potential cellular rejuvenation therapeutic approaches (gene therapy, small molecule) towards targeting these mechanisms.

Epigenetics, DNA hypermethylation and Alzheimer's Disease

Epigenetics is the study of how positive and negative lifestyle factors (exercise, smoking, drinking, etc.), aging, disease, and injury all influence how effectively our genes work. Epigenetic changes include methylation and hydroxymethylation of DNA cytosine residues and post-translational histone modifications such as lysine acetylation and methylation that are primarily positioned at the N-terminal histone tails protruding from the nucleosome core (18, 19). During aging, epigenetic marks (e.g., DNA methylation) occur on DNA triggering changes in the pattern of gene expression (18, 19). These epigenetic changes accumulate during one's lifespan and can lead to vast alterations in gene expression with critical genes being repressed or overexpressed (18, 19). This is particularly true when assessing neurodegenerative pathologies as epigenetic modifications have been shown to have a negative impact on cognitive ability (18, 20) and AD-related cognitive and pathological parameters (21–29). HDAC inhibitors (including nicotinamide and valproic acid) show promise in neurodegeneration and AD (30) and represent a potential epigenetic therapeutic approach.

AD is a complex disease with respect to epigenetic changes with evidence supporting both DNA hypermethylation and hypomethylation (21–29). In general, altered DNA methylation correlates with AD pathology including increased Aβ load, amyloid neuritic plaques, increased tau neurofibrillary tangle density, and an association with APOe4-positive status as well as increased cortical pathology (21, 31–38). De Jager et al. report that of the 71 differentially methylated regions (DMRs) identified in AD, 82% are in the direction of hypermethylation and Semick et al. reported that of 858 DMRs, 57% were due to hypermethylation (22, 39). While both hypo- and hypermethylation are relevant to AD, this review is largely focused on the consequences of DNA hypermethylation.

In AD patients, there is a strong association between age-acceleration and AD risk factors including body mass index, total cholesterol to high-density lipoprotein cholesterol ratios, socioeconomic status, high blood pressure, and smoking behavior (40). These risk factors are well known to accelerate epigenetic aging (41, 42). The relationship between epigenetic changes and chronological aging has been well established with increases in DNA methylation (DNAme) occurring with advancing age as measured by multiple blood-based DNAme clocks (36, 43–46). As this field has rapidly developed, numerous DNAme clocks have emerged based on specific tissue types, including a cortical DNAme clock described by Shireby et al (47). Associations between DNAme on CpG islands (peripheral blood, brain) and AD progression suggest a role for these epigenetic mechanisms in driving AD pathology (48–50). Increased DNAme age in the dorsolateral prefrontal cortex is associated with elevations in diffuse plaques, neuritic plaques, amyloid load and with a decline in global cognitive functioning, episodic memory and working memory in patients with AD (51). Multiple DNAme epigenetic clocks (Hannum, Horvath, PhenoAge and Cortical) show a relationship between DNAme age, a diagnosis of AD, and Aβ load with the Cortical clock showing stronger associations to a diagnosis of AD and Aβ load (52). The Cortical clock is also associated with tau tangles and neocortical Lewy body pathology which are linked to AD symptoms including dementia and cognitive decline (52). The PhenoAge clock shows that the dorsolateral prefrontal cortex (DLPFX) of AD patients is older than age-matched controls and are associated with amyloid load, neuritic plaques, and neurofibrillary tangles (53). Corresponding with the epigenetic changes observed in AD, the transgenic 5XFAD mice show age-acceleration (54). Similarly, the 3xTg-AD mouse shows increased DNAme using mouse cortical and hippocampal based clocks with CpGs enriched in genes related to aging, neuronal activity, and neurodegeneration (55).

There are numerous reports of genes near hypermethylated sites that are related to AD. A differentially methylated region (DMR) of the ankyrin 1 (ANK1) gene is associated with entorhinal, superior temporal gyrus, prefrontal, and frontal cortical neuropathology (36, 43–46). Increases in prefrontal cortical CpG DNAme sites are associated with pathological AD including increased Aβ load and tau tangle density with changes in genes for SORL1, HLA-

DRB5, SLC24A4, and BIN1 (36, 43–46). Methylation at multiple CpG sites in the ABCA7 locus is significantly linked to amyloid deposition and changes in brain morphology (35, 56). The SERPINF1 and 2 genes as well as CDH23, DIP2A, RHBDF2, RPL13, and RNF34 are located near CpG methylation changes (22, 26). Additional AD hypermethylated DNA sites include ANKRD30B, DUSP22, and CSNK1G2 with differentially methylated regions near genes involved in cell adhesion, immunity, calcium binding, and with DUSP22 playing a role in tau phosphorylation and CREB signaling (26, 33). APOe4 is a well-known risk gene for developing AD (57). The APOe4 gene contains a fully methylated CpG-island suggesting that epigenetic changes may also impact AD pathology (31). AD brains show hypermethylation of CpG islands for BDNF and cAMP response-element binding protein (58). DNA hypermethylation of the BDNF promoter plays a role in the development of MCI and progression to AD (59). Reduced cognitive ability and reductions in brain cortical volume and thickness in frontal, anterior lateral, and medial temporal lobes are associated with increased DNAme C-reactive protein corresponding with effects on inflammation (60, 61). Oxytocin is hypermethylated in blood and hypomethylated in the middle temporal gyrus (62). Further evaluation revealed regulation of brain DNAme for oxytocin was varied across AD progression with hypermethylation of middle temporal gyrus oxytocin at the Braak 3-4 stages (62). Not only are there differentially methylated regions but there are also differentially regulated hydroxymethylated regions in both brain and blood with associations to AD (62). Increased hydroxymethylation of the acetylcholine nicotinic receptor CHRNB1 was observed in AD cases (62). Distinguishing overall DNA methylation from those more specifically on CpG islands will certainly impact interpretation and treatment strategies. Overall, these data reflect that there are numerous genes associated with AD progression and pathology that are epigenetically regulated. Future treatment controlling DNA methylation may be a more successful approach for the treatment of AD than discretely targeted therapeutics for each individual gene.

Partial Epigenetic Reprogramming

One of the most promising strategies to cellular rejuvenation utilizes epigenetic reprogramming. Gene therapy has been gaining popularity, with approaches to treat a wide range of diseases currently under development or already approved (Luxterna – retinal dystrophy, Zolgensma – spinal muscular atrophy, Hemgenix – hemophilia B, Elevidys – Duchenne muscular dystrophy, and Roctavian – hemophilia A). Unlike typical gene therapy approaches that introduce a functional copy of the defective gene of interest (gene replacement) or alter the sequence of existing genes (gene editing), epigenetic reprogramming focuses on restoring cells to a more youthful state by altering the epigenetic changes that are repressing gene function. Dr. Shinya Yamanaka's Nobel Prize winning discovery that the expression of four transcription factors Oct4, Sox2, Klf4, and cMyc; collectively called OSKM, could return a cell state back to a pluripotent stem cell by removing epigenetic marks was a foundational advancement in the field making an epigenetic therapeutic approach possible (63).

Recent studies have investigated the effects of OSKM and OSK (only three transcription factor genes Oct4, Sox2 and Klf4) on activity in brain and neural retina. Several studies have analyzed the effects of OSKM in the brain and on learning and memory. Multiple delivery systems have been used to enable the in vivo expression of either OSKM or OSK, including both Tet-off (OSKM or OSK continuously expressed); (64, 65) or Tet-on (rtTA-inducible expression system with OSKM or OSK only expressed after systemic administration of doxycycline (DOX) (66–69). OSKM and OSK can either be delivered to their target via administration of a vector (e.g., AAV2 or adenovirus (64, 65, 69) or in a transgenic mouse containing rtTA and a doxycycline-inducible cassette containing OSKM (66, 67). The DOX driven regulation of the Tet-on system allows for expression of the transcription factors as needed, enabling better control of timing of expression to maximize therapeutic benefit.

Full expression of Yamanaka factors via cyclic administration of DOX to transgenic mice with a DOX-controlled inducible OSKM expression system have been shown to produce increased levels of neurogenic markers and the NMDA receptor subunit GluN2B as well as improved memory in an object recognition task (66). Intrahippocampal administration of an adenovirus-OSKM improved learning in old rats in a Barnes maze task with trends towards improvements in memory as well (65). A subset of hippocampal hypermethylated CpG sites were demethylated by AAV-OSKM potentially allowing for restored expression of genes associated with cognition (65). The limiting factor for therapeutic efficacy with the use of all four Yamanka factors (OSKM), however, is that cell identity is erased, and tumor formation or negative effects can occur (70, 71). While short-term or cyclical expression of OSKM may be able to avoid tumor formation (72), the use of OSKM clinically remains potentially concerning due to these known toxicological concerns.

Using partial epigenetic reprogramming to express only three transcription factor genes (Oct4, Sox2 and Klf4; collectively called OSK) and removing the oncogenic cMyc, allows cells to be returned to a more youthful state while maintaining their original cellular identity without teratoma formation (64). In this regard, intravenous administration of AAV9-OSK followed by 10 months of gene induction by DOX did not increase tumor incidence or had negative effects on overall health in mice up to 32 months of age (64). AAV2-OSK has

been used to reprogram retinal ganglion cells (RGC) in the neural retina and demonstrated efficacy in mouse models of aging, optic nerve crush, and glaucoma (64). To that end, intravitreal (IVT) administration of AAV2-OSK improves vision (measured by optomotor reflex) and visual function (measured by pattern electroretinogram; pERG), reverses DNA hypermethylation, promotes axon regeneration, and RGC survival after optic nerve injury (64). More recently, we evaluated the effects of OSK in a nonhuman primate (NHP) model of non-arteritic anterior ischemic optic neuropathy, NAION, (model initially described by Chen et al., 2008). In this model, a DOX-controlled inducible form of AAV2-OSK was administered IVT to the NHPs one day post laser injury and reversed the laser-induced deficits in pERG consistent with restoration of visual function (69). Systemic administration of a DOX controlled inducible AAV9-OSK has been shown to extend lifespan in old mice (73). Interestingly, the Sinclair lab developed mice with inducible changes in epigenome (ICE) that results in acceleration of aging across multiple organ systems including the brain (74). The acceleration of aging occurs at physiological, cognitive, and molecular levels, including erosion of the epigenetic landscape, cellular ex-differentiation, senescence, and advancement of the DNA methylation clock (74). ICE mice have impaired memory (contextual fear conditioning and Barnes maze) and more activated astrocytes and microglia in hippocampus (74) supporting the idea that impaired memory and neurodegeneration are related to epigenetic changes associated with erosion of the epigenetic landscape. Consistent with the beneficial effects of OSK on RGCs in optic nerve crush, glaucoma, aging, and NAION models, IVT administration of AAV2-OSK to the ICE mice restored RGC mRNA levels to a more youthful pattern (74). These studies serve as proof of concept that partial epigenetic reprogramming results in cellular rejuvenation associated with reversal of DNA hypermethylation and can promote axon regeneration. Collectively, these results suggest that OSK may also be effective in neurodegenerative disorders such as AD by modifying the epigenetic landscape in the brain.

Delivery of gene therapies for the treatment of Alzheimer's disease will be challenging. Multiple factors need to be addressed including localization of the genes of interest to brain without excessive expression in non-target organs (e.g., liver), sufficient brain penetration to induce necessary expression for therapeutic efficacy and ensuring an appropriate safety profile. With respect to AAV gene therapies that only require a single administration, options like injection directly to the cisterna magna (75) or a surgical stereotactic localized approach (e.g., intrahippocampal) could be considered. Alternatively, identifying appropriate systemic viral delivery systems which increase brain penetrance and preferably reduce liver expression (76, 77) or newer delivery systems that will target the brain with sufficient delivery of the gene(s) of interest may prove effective. Encouraging initial data from studies directly administering Yamanaka factors resulting in cellular rejuvenation suggests that the ongoing improvements in delivery systems will facilitate the development of this new class of therapeutics.

Chaperone Mediated Autophagy

There are multiple forms of autophagy, including macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA), which are critically involved in aging and proteostasis and play a role in neurodegeneration (14, 15, 78, 79) another approach to cellular rejuvenation through the removal of specific proteins that increase or aggregate during neurodegenerative disease (14, 15, 74, 75). CMA is initiated when a KFERQ motif on a substrate protein is recognized by the constitutively active heat shock cognate protein of 70 kDa (Hsc70) (80). Once bound, the protein can then associate with the cytosolic tail of the LAMP2A receptor leading to multimerization of LAMP2A into a translocation complex on the lysosome to facilitate the chaperoning of the unfolded protein into the lysosome (81–83). Once in the lysosome, the protein can be degraded by lysosomal enzymes (84–86). Impairments in the CMA system may reduce or limit proteins from entering the lysosome and being degraded leading to elevations in proteins that may become aggregated and toxic, particularly in neurodegenerative diseases (80-82). Forty percent of proteins contain a KFERQ motif and are subject to proteostasis via CMA (80). Cuervo and Dice demonstrated that CMA is reduced in aging (87) and others have shown CMA in the brain is impaired in several neurodegenerative diseases including AD, Parkinson's disease (PD), and Huntington's Disease (88). Additionally, it has been shown that relevant proteins in these indications such as amyloid precursor protein (APP), tau, a-synuclein, LRKK2, and huntingtin containing the KFERQ motif are needed for CMA (89–94). With the rapidly growing understanding of the role of CMA in neurodegenerative diseases and the identification of compounds that activate CMA, there are now opportunities to develop CMA activators for the treatment of neurodegenerative diseases including AD and PD. CMA activators will enable cellular rejuvenation by increasing proteostasis and preventing aggregation of toxic proteins.

To assess the role of neuronal CMA, Cuervo's group knocked out (KO) the LAMP2A receptor in both whole body (L2A KO) and in a neuronal specific manner (CKL2A KO) (95). Deficits on cognitive and motor function were observed in both KO models (95). Accumulation of multiple protein types in the cortex and hippocampus in the insoluble fraction suggests that reduction of CMA results in marked impairments of neuronal proteostasis (95). Proteins containing a KFERQ

motif were more likely to be enriched consistent with the impaired CMA (95). These results confirm a role for CMA in CNS homeostasis and suggest that impairment in CMA may play a role in neurodegenerative disorders.

Role of CMA in AD Pathologies

Key proteins associated with AD pathology include both amyloid and tau (4–9). APP processing plays a critical role in the formation of beta amyloid (96). APP contains a KFERQ motif at its C-terminus suggesting that APP may be degraded via CMA (97). Deletion of the KFERQ domain results in impaired processing of APP and results in increases in C-terminal fragments (CTFs) and secreted n-terminal fragments of APP (97). Increased APP-CTFs lead to enhanced tau phosphorylation consistent with AD pathology (97).

Therapeutics focused on addressing tau pathology are a critical part of the AD landscape (98). Tau contains a KFERQ motif and Wang et al. demonstrated that degradation of wild type tau is CMA-dependent (94). However, a mutant form of tau (TauRDΔK280) found in frontotemporal disorder is partially cleaved retaining KFERQ motifs. These cleaved fragments associate with LAMP2A but cannot be fully translocated into the lysosome (94). The inefficient translocation of the tau fragments across the lysosomal membrane leads to formation of tau oligomers at the surface of these organelles which may promote oligomerization and aggregation of mutant tau (94). Building on those findings, Caballero et al. showed that neuronal tau is degraded by CMA whereas acetylated tau inhibits CMA (99). Like mutant tau, acetylated tau associates with the LAMP2A receptor but prevents substrate translocation into lysosomes thereby allowing it to build up and aggregate (99). Acetylated tau also increases tau propagation in the L2AKO mice (99) consistent with the tau propagation observed in AD (98). Taken together, these results suggest that mutant and acetylated tau reductions in CMA lead to elevations in tau fragments and acetylated tau which in turn increases oligomers and tau propagation.

Further characterizing the impact of CMA in AD models, a marked impairment in CMA can be observed in a mouse model expressing mutant human tau (hTauP301L) (95). To further impact CMA in a mouse AD model, Cuervo's group crossed the LAMP2A KO mice with a triple transgenic (TauPS2APP mouse) (95). The exacerbation of the CMA deficit led to a marked increase in Aβ deposition and an accumulation of phosphorylated tau, aggregated tau and S422 phosphorylated tau (95). The total amount of APP is not increased, but there is an increase in APP CTFs and Ab42 peptide (95), consistent with the findings from deleting the KFERQ domain of APP (97). These data are suggestive of impairments in CMA in AD mouse models that are further exacerbated and accelerated by reductions in LAMP2A.

Although it gets less attention than amyloid and tau, elevations in RCAN1 are observed in patients with AD (100, 101). RCAN1 contains a KFERQ motif consistent with its degradation occurring, in part, via CMA (102). To that end, reducing CMA activity leads to increased levels of RCAN1 (103). CMA is reduced in both excitatory and inhibitory neurons as AD progresses through middle and late Braak staging (95) consistent with elevations in RCAN1. Increased RCAN1 leads to increased tau phosphorylation, consistent with the elevations in phosphorylated tau in AD (104). The impact of impaired CMA on accumulation and aggregation of proteins associated with AD suggests that CMA activators may have therapeutic benefit in the treatment of AD and other neurodegenerative disorders.

CMA Activators

Recently, several compounds demonstrating CMA activation have been identified (95, 105, 106). The CMA activators CA77.1, metformin, and PRO-Br have been evaluated in the mouse models of tauopathy and AD (95, 105, 106) with similar findings. Trehalose and lactulose also increase CMA and have shown efficacy in a model of intrahippocampal CA1 injection of oligomeric Aβ25–35 (107).

CA77.1 belongs to a class of compounds that activate CMA by stabilizing the interaction between RARα and N-CoR1 (108). In PS19 transgenic mice which express tau with the frontotemporal dementia mutation P301S, CA77.1 decreases pS19 hyperactivity and reduces the levels and number of neurons containing pathogenic tau in the hippocampus, amygdala, and piriform cortex. There is less aggressive tau pathology in the hippocampus of CA77.1-treated mice and lower levels of S422 and AT8 phosphorylated, oligomeric, and insoluble forms of tau (95). In the triple transgenic mice TauPS2APP, administration of CA77.1 improves visual memory, and reduces β-amyloid (immature and mature plaques) and tau-related pathologies (reduced early T231 pTau) in the hippocampus and cortex (95).

Metformin, a drug used to treat diabetes with multiple modes of action including both AMPK dependent and independent mechanisms (109), enhances activation of CMA via a TAK-1-IKKa/b signaling pathway involving phosphorylation of Ser85 of Hsc70 (105). Metformin prevents cytotoxicity associated with overexpression of both WT and K595N/M96L APP mutants by enhancing CMA-mediated degradation (105). In APP/PSI mice, administration of metformin improves learning and memory in the Morris water maze, decreases insoluble Ab1-42 in whole brain, reduces hippocampal Aβ plaques, and reduces APP protein levels (105). Metformin reversed the microglial autophagy impairment, increased the number of microglia around Aβ plaques, promoted the phagocytosis of tau, and reduced Aβ load and tau pathology in APP/PS1 mice injected intrahippocampally

with brain extracts containing tau aggregates (110). The relationship of these effects to metformin's known effects on glucose and insulin need to be further investigated.

PRO-Br is an HDAC6 inhibitor that activates CMA (106). PRO-Br enhances expression of LAMP2A and Hsc70, reduces pathogenic hyperphosphorylated tau clumps, increases dendritic spines, and improves memory function in 3xTg-AD and P301S tau mice models. PRO-Br reduced expression of the sarkosyl-insoluble pTau variants (106). PRO-Br links both epigenetic mechanisms and CMA.

Trehalose and lactulose are disaccharide prebiotocs that activate autophagy pathways including CMA (107). Both trehalose and lactulose attenuate short-term memory and learning retrieval deficits in mice with a bilateral intrahippocampal CA1 injection of oligomeric Aβ25–35 (107). Trehalose and lactulose also decreased neuroinflammation and increased the levels of the autophagic pathways including CMA (107).

Screening for small molecule CMA activators using functional screening will require understanding of the potential mechanisms by which compounds demonstrate CMA activation. Thorough examination of the CMA cascade of events will be necessary to understand how a compound is influencing CMA. As with all small molecules for CNS indications, compounds will need to be brain penetrant and highly bioavailable. Trehalose is reported to have effects on autophagy, including CMA, and is currently being evaluated using oral administration in a PD clinical trial (NCT05355064).

Conclusion

The newest AD therapies are just the beginning of novel treatments for AD. The unmet need across all stages of the disease remains high. The next wave of potential therapeutics for AD is emerging and cellular rejuvenation approaches will be important for disease modifying treatments. Moreover, cellular rejuvenation therapeutics may work effectively in conjunction with the current AD therapeutics to facilitate regeneration of neurons impaired by disease. Advancements in partial epigenetic reprogramming and in the identification of CMA activators make these cellular rejuvenation technologies an exciting opportunity.

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