RECIPROCAL INTERACTIONS BETWEEN TAU AND MICROGLIAL SENESCENCE DURING THE DEVELOPMENT OF ALZHEIMER-LIKE PATHOLOGY IN MOUSE MODELS

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ABSTRACT

This review explores Alzheimer's Disease (AD) and Frontotemporal Dementia (FTD) focusing on the complex pathophysiology, advanced diagnostic methodologies, and emerging therapeutic strategies. It synthesizes a wide array of studies to elucidate the molecular, cellular, and systemic changes characteristic of these disorders. Additionally, the review examines the socio-economic impacts and caregiver burden associated with these diseases, highlighting the need for innovative approaches in treatment and care. The effect of cellular senescence on the progression of disease pathology and symptomology; markers and mechanisms of senescence are identified and explored in this review. The document aims to provide an in-depth analysis, identify gaps in current knowledge, and propose directions for future research.

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INTRODUCTION

Alzheimer's Disease (AD) is a neurodegenerative disease characterized by the progressive deterioration of neurons by two protein aggregates Tau and Amyloid beta. The path of neuronal deterioration, the timing of memory loss, and cognitive impairment distinguish this dementia from other Tauopathies. Fronto-temporal dementia (FTD) is a Tauopathy hallmarked by its onset and progression in the frontal and temporal lobes. The disease is also most recognized for its degenerative impact on executive function and patients' regulation of inhibition (Magrath Guimet et al. 2021). Unlike AD FTD is characterized by the presence of Tau without amyloid beta(Bang et al. 2015). Both diseases are forms of dementia. Dementia is an umbrella term that defines a person struggling with a group of conditions that include memory and judgment impairments (Livingston et al. 2020).

CHAPTER 1: *Clinical Diagnostic Features, Demographics, and Societal Impact*

In AD there are seven stages of disease *(Figure 1).* These stages are illustrative hallmarks to break down when symptoms progress. Stage one occurs before clinical diagnosis (Manca et al. 2023). Stage two occurs when pathological changes are beginning to occur but there is no forgetfulness or memory loss. Stage 3 is characterized by the subjective cognitive decline (Delacourte et al. 1999). Deficits in AD are often seen in patients' daily activities, exemplified by the four A's of AD: Amnesia (the loss of memory), Aphasia, (the loss of the ability to understand or express speech), Apraxia, (the inability to carry out tasks despite the physical capability), and Agnosia (the inability to recognize things)(Burns 2000). Mild cognitive impairment characterizes Stage 4. The greatest difference between stages 3 and 4 is the frequency of cognitive strain becomes more noticeable. There is a neuropsychiatric component of AD that coincides with alterations in cognition. These symptoms are called behavioral and psychological symptoms of dementia (BPSD). BPSD symptoms include vast oscillations in mood that fluctuate from feelings of depression to feelings of apathy or anxiety. It is common for patients to exhibit clinical delusions and disorientation accompanied by changes in appetite and sleep which can augment disinhibition and agitation (Cerejeira et al. 2012). Decreased independence is often seen in Stage five. Recently path integration (PI) has been of interest as an early behavioral symptom. It examines a patient's ability to spatially navigate cues, orient themselves in their environment, to regulate, and adapt their motions given their estimated environment. While PI scores are not directly linked to a BPSD, they can be clinically used as a diagnostic screening tool for early prevention as PI correlates with cerebrospinal fluid Tau (Howett et al. 2019). Patients in stage six require continuous care. In stage seven lack of physical control, such as incontinence, illustrates the severity of cognitive impairment in the late stages of disease and the terminality of the dementia care state. These stages serve as a tool to help people understand what they're going through and a guide to help them adjust and cope with their disease progression. Not everyone progresses through the steps at the same rate, but they can be used to examine how their prognosis is developing. When a patient starts to present Mild Cognitive Impairments (MCI) the physician must first determine if the onset is due to Alzheimer's Disease (AD), frontotemporal

dementia (FTD), or another form of dementia. The cognitive impairments in AD and FTD do not coincide with motor impairments (McKhann et al. 1984).

In AD, the three cardinal diagnostic features must be present for a true diagnosis, cognitive impairment, Tau, and amyloid beta. While patients are alive physicians and neuropsychologists can distinguish AD from other dementias by observing criteria in the diagnostic battery and examining physical and clinical manifestations. In AD tests like the Mini-Mental State Examination (MMSE), and the Montreal Cognitive Assessment (MocA) are imperative to gauging cognitive state and disease progression (De Jager et al. 2003)(“Parkinson’s Disease and Braak stages - Neurotorium” n.d.) . The MMSE audits cognition by assessing the patient’s orientation, registration, attention, calculation, recall, and language.(Shefet and Lurie 2024) The MocA assesses short-term memory recall and visuospatial abilities through clock drawing, executive function, phonemic fluency, and verbal abstraction. (“| MoCA Fact Sheet” n.d.) (Maust et al. 2012) These are all cognitive impairments that come after disease onset.

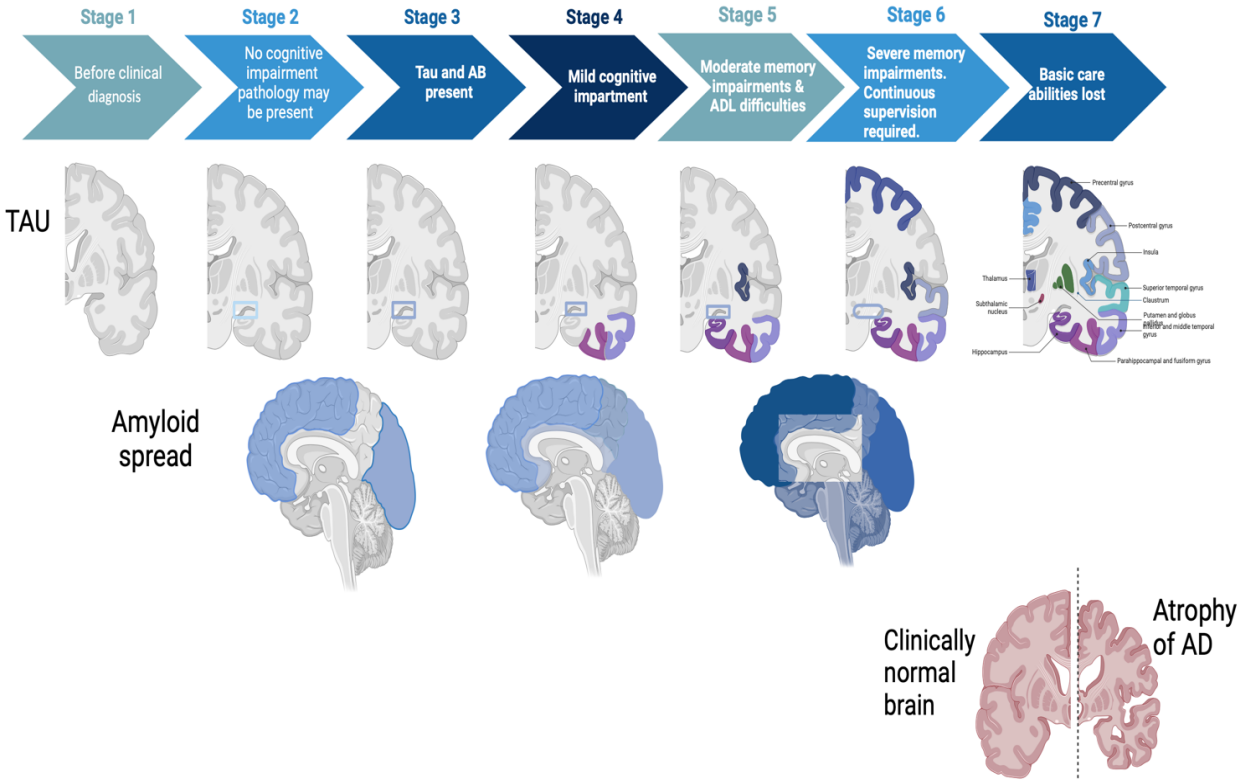

Figure 1: A comparative reference of symptomological, pathological, and phenotypic progression of Tau and amyloid in AD. The timeline (blue arrows in row 1) indicates stages of symptomology, clinical impact, and lasting cognitive decline. The corresponding brains demonstrate when Tau seeds and progresses through the brain at each stage outlined (row 2). The location of tau pathology is indicated by colored shading in these brain hemispheres. Amyloid spreads thoroughly early in the disease process and this is illustrated in row 3. The blue color indicates the location of amyloid pathology at different stages. The intensity of the blue color indicates the amount of amyloid pathology in a given region. Lastly, atrophy of the cortical and temporal lobes results in widened sulci, enlarged ventricles, and mass reduction (row 4). Figure generated using BioRender.

Braak Staging is a silver staining process post-mortem for Tau pathology (Gallyas 1971; Dallaire-Théroux et al. 2019). The hyperphosphorylation and dysregulation of Tau leads to Tau polymerization and aggregation(Metaxas and Kempf 2016). This aggregation Tau pathology consists of Neurofibrillary tangles (NFTs). NFTs are composed of the Microtubule-associated protein Tau (MAPT), commonly called Tau for short (Metaxas and Kempf 2016). Braak staging reflects the spread of Tau throughout the brain in a numerically based system. This system is based on the expansion of lesions. The staging characterizes neuronal changes in the entorhinal cortex and temporal lobe. The use of Braak staging has been applied to PET scans to observe Tau progression (St-Onge et al. 2023). Tau staining is first seen in the hippocampus and entorhinal region (Braak stages 1 and 2) and then progresses throughout the cortical regions as the Braak stage increases (Braak et al. 1993). In later Braak stages III IV amyloid plaque burden increases to become sufficient for dementia pathology in AD (Hyman et al. 2012; Therriault et al. 2022). These extracellular proteins are made up of β-amyloid (Aβ) peptides. Aβ plaques are thought to be an early indicator of AD, as they spread far before clinical symptoms appear(Dubois et al. 2016). In AD patients Aβ plaques first appear in the neocortex, then spread to.limbic regions, subcortical areas, and eventually the brainstem and cerebellum. NFTs start to appear later than Aβ and start in the transentorhinal and entorhinal cortex and the hippocampus (Dubois et al. 2016) In stages 3 and 4 Tau spreads throughout the limbic system and by stages 5 and 6 it overwhelms the cortices.

Although the disease was named after Dr. Alois Alzheimer, the neuropathologist who characterized the disease, it was discovered in a woman, Auguste Deter. At the time the mere recognition of the disease was novel but in retrospect, it makes sense as AD is more prevalent in women. Two-thirds of the American AD population are women(“2024 Alzheimer’s disease facts and figures.” 2024). Gender is also a leading risk factor in AD, women over 45 are twice as likely as men to develop AD (“2024 Alzheimer’s disease facts and figures.” 2024). There is a lot of debate about the use of sex hormone therapies as chronic use has shown potential for cognitive decline. For example, estrogen-containing therapies for menopause or birth control; or an androgen deprivation therapy for prostate cancer are both examples of contentious risk factors (Shumaker et al. 2004; Barry et al. 2006). Although both men and women

develop neuritic plaques, the density at which women experience pathology is greater and causes more cognitive dysfunction and degeneration(St-Onge et al. 2023).

An estimated 6.8 million Americans are living with Alzheimer's disease("2024 Alzheimer's disease facts and figures." 2024). Proportionally AD affects twice as many African American and Hispanic elderly adults than their Caucasian counterparts(Yaffe et al. 2013). These statistics inadequately account for the relationship between the prevalence and incidence of the disease. Socioeconomic factors are thought to contribute to African Americans having a higher prevalence. Disparities are founded on structural racism. This racism is pervasive and a stressor thus becoming a risk factor for dementia(Bailey et al. 2021). The influence of structural racism compounds over a lifetime and accompanied by a patient's comorbidities and early life experiences can lead to detrimental cognitive and physical outcomes (Bailey et al. 2017). Although often considered Caucasian, Ashkenazi Jews appear to have a genetic risk factor higher than the average Caucasian. This is due to the " founder effect" where their limited genetic variation, led to a higher prevalence of genetic risk factors(Li et al. 2023). In a GWAS study, there were several carriers of both the APOE and TREM2 alleles within the population(Li et al. 2023).

In individuals with disease, caregiving is often a considerable emotional expense and often becomes a familial burden. As the annual cost of hospice and memory care averages $17,717 (95% CI: $15 475, $19 788)(White et al. 2019), (Rice et al. 2001)after financial assistance programs. The economic burden of the disease grows as diagnoses progress. The financial burden associated with AD has cost Medicare $321 billion in 2022 and is projected to grow to an expenditure of 1 trillion by 2050 with the aging population(Skaria 2022). These forecasted costs are not unrealistic as there is already a growing demand for primary care physicians (PCP), geneticists, neurologists, psychiatrists, nurse practitioners, registered nurses, social workers, and direct care technicians. There has been a global shortage in the healthcare workforce since 2016, leading to an imbalance in skilled labor and a shortage of personnel (Džakula and Relić 2022). To rectify this imbalance the World Health Organization (WHO) sent out a memorandum to try to encourage more physicians to become PCP, as it was found that PCP made most dementia diagnoses(Workforce n.d.), (Liss et al. 2021). These licensed necessary supporting caretakers are just the

tip of the diagnostic and supportive care network needed to alleviate the burden of the strain of disease pathology through progression. The average American family cannot afford the cost of care before or after Medicaid and Medicare assistance, this often leaves a large informal or familial cost on caregivers in the form of significant time and energy. It's estimated that 18.4 billion hours of unpaid caregiving hours are performed by family members ("2024 Alzheimer's disease facts and figures." 2024). This has been reported as leading to feelings of stress, captivity overload, and strain in the caregiving relationship(Fisher et al. 2011) .

While the pathology of both diseases display Tau, only AD has amyloid beta. FTD has 2 cardinal hallmarks, the presentation of behavioral disinhibition and Tau. The histopathology and other clinical diagnostics tests can be done by analyzing Tau and amyloid burden. In FTD two quantifiable proteins that contribute to Tau pathology are TDP-43, and FUS (Mackenzie and Neumann 2016). TAR DNA binding protein 43 (TDP-43) aggregates can be observed and quantified (Jo et al. 2020). TDP-43 is a ubiquitously expressed protein that hyperphosphorylates and ubiquitinates under pathological conditions of Tau (Arai et al. 2006; Hasegawa et al. 2008). TDP-43 travels from cell to cell via cytoplasm with prion-like properties Just like(Nonaka et al. 2013). The RNA-binding protein, Fused in Sarcoma (FUS) normally maintains cellular fusion, alternative splicing, and transcription(Ishigaki and Sobue 2018). A definitive diagnosis of AD is post-mortem and requires histopathology that examines neurofibrillary tangles (NFTs) and amyloid beta plaques (Aβ)(Handen and Christian 2022). Although definitive diagnoses are made at death, clinically there are quantifiable ways to make preliminary diagnoses.

Clinically, there are a few measurable substances that can indicate a change in patient outcomes, these readouts are called biomarkers. Biomarkers enable great speed, precision, and efficiency in patient data collection (Califf 2018). They also introduce a level of statistical reliability in measurement with reproducible validity. The more commercially available biomarkers become, the more accessible care can become to the masses. Biomarkers also enable earlier diagnosis with more detailed diagnosis. The more precise the diagnosis the better the care can be tailored to the patient and the better the prognosis can be for patient outcomes. Biomarkers identifying patients' predeath could aid in preventative aspects of the

disease. If patients could identify risk for diseases before pathology onset that could be a groundbreaking step. Predictive biomarkers could help those with familial AD or those in high-risk groups mitigate their comorbidities. Currently, three types of biomarkers exist commercially: blood biomarkers, CSF, and PET ligands. To detect AD Tau and Aβ, Lilly manufactures blood biomarkers for P-Tau, NFL (Neurofilament light chain), and GFAP (Teunissen et al. 2022). These biomarkers are being tested to see if they can be relied on as predictive biomarkers when pulled from blood but as of right now, clinical studies have not concluded(Hampel et al. 2018).

The cerebrospinal fluid has two primary quantifications, the measurement of the ratio of total Tau to p-Tau and the ratio of Aβ42/Aβ40(Blennow et al. 2023). Neurofilament light chain protein in cerebrospinal fluid (CSF) can detect levels of axonal damage in AD. There are also PET imaging ligands for amyloid and Tau which are commercially available (Jack et al. 2018). Clinically this pathology can be detected in histopathology predeath to some extent via PET scans and MRI. These imaging methods can detect Tau burden with biomarkers and tracers like ^{18}F-THK523 but they cannot bind to Aβ and cannot give a full picture of cognitive impairment as it has high white matter retention so it doesn't penetrate well in vevo (Dani et al. 2016). Tau PET imaging is very successful and tracers like ^{18}FflorTaucipir, ^{18}F-MK6240, ^{18}F-RO948, and ^{18}F-PI2620 bind with high efficacy and are widely used and map Tau progression with Braak staging (Tagai et al. 2021; Bischof et al. 2021). Amyloid tracing is weaker as Off-target binding generally occurs with amyloid ligands (Groot et al. 2022). Diagnostic tools are ultimately up to the physician's discretion. There are arguments for the validity and comparability of blood biomarkers and CSF markers. Ultimately, one has to be accompanied by PET ligands of Tau as it gives the most complete view of disease progression.

The behavioral symptoms at the onset of AD present differently from those of FTD. FTD patients often present with decreased inhibition, lack of judgment, impaired interpersonal skills, lack of empathy, and increased impulsive and compulsive behaviors. The degeneration in their frontal lobe and aggregation of Tau compounds the cognitive impairment in executive function. The key diagnostic difference between the two types of dementia is the onset and pronouncement of behavioral disinhibition.

In FTD a patient changes in personality, language presentation, and behavior so they become so dysregulated, disruptive, or unacceptable that they are unlike their prior personalities. In AD disinhibition is often milder as a result of neurodegeneration and takes the form of impulsivity. This impulsivity can result in morbid betting, kleptomania, overeating, violence, or any unplanned action that is in response to an external source (Moeller et al. 2001). This often necessitates the role of a caregiver to help mediate these behaviors.

In FTD individuals who are affected are typically between the ages of 45-and 65 -years -old. There's also equal prevalence in both women and men in FTD, unlike AD where there is a higher prevalence in women(Bang et al. 2015). The impact of FTD is particularly significant because it affects working-age adults, leading to loss of employment and financial instability(Bang et al. 2015). While those affected develop FTD younger, the condition can often progress rapidly, with atrophy and degeneration. On average, the lifespan post-diagnosis was reported to be between 5-6 years (Davies et al. 2006).

CHAPTER 2: *Neurocircuitry*

AD impacts brain circuitry involving the hippocampus, entorhinal cortex, and neocortex, with significant effects on learning and memory (Haass and Selkoe 2007). The disease progression involves selective vulnerability of specific neuronal populations, with widespread cortical atrophy in the later stages (Haass and Selkoe 2007). Neurons within the cholinergic system are the subpopulations that become affected by neurodegeneration resulting in patients experiencing cognitive deficits. The effects of Acetylcholine (ACh) receptors not transducing their G protein interaction through their ligand-gated channels with high calcium permeability(Levin and Rose 1995). This dysregulation of the cholinergic neurons can also be due to mitochondrial dysfunction (Wong et al. 2020). These cholinergic neurons in AD innervate the basal forebrain. When labeled with choline acetyltransferase (ChAT)), the perikarya can be detected in the caudate and putamen, the magnocellular basal nucleus, the nucleus accumbens, the olfactory tubercle, and the cranial nerve motor nuclei(Armstrong et al. 1983). It has been found that abnormal cholinergic changes affect epigenetic markers like PSEN1 and phosphorylation levels of Tau, impacting cognitive impairment (Ramos-Rodriguez et al. 2013; Campanari et al. 2014). While the cholinergic system is imperative for regulating neurogenesis and synaptic plasticity, it also is an integral component of the neuron's neuroprotection system (McKinney et al. 2004).

FTD affects brain circuitry in the frontal and temporal lobes, impacting executive function, behavior, and language networks. To clinically examine the deficit in FTD NFL can be measured in CSF and blood; Fluorodeoxyglucose positron emission tracer (FDG) PET imaging of Tau and TDP-43; and genetic testing for mutations in MAPT, GRN, and C9orf72 (Ntymenou et al. 2021).

CHAPTER 3: *Tau*

Tubulin-associated unit (Tau) is a microtubule-associated protein encoded by the gene (*MAPT*). MAPT is located on chromosome 17 in humans and has 6 isoforms when transcribed. The human Tau gene is encoded by 16 exons that undergo alternative splicing. The alternative splicing can include or exclude exons 2,3 or 10 depending on the isoform (Avila et al. 2016). Transcripts that contain exon 10 have an additional microtubule-binding domain. They are known as the 4R repeats; the other isoforms which exclude exon 10 are known as the 3R repeats. Tau's primary responsibility is stabilizing microtubules and ensuring cell polarization in the differentiation of neurons (Mandelkow and Mandelkow 2012). This is why 4R repeats utilize Tau's microtubule stabilization. Exons 2 and 3 might play a role in axonal structural support and microtubular and axonal arrangement(Amos 2004). Their inclusion enables the isoform to change the length of the end terminal domain which could impact Tau interactions and binding partners (Derisbourg et al. 2015). Exons 1, 4, 5, 7, 9, 11, 12, and 13 are foundational exons that give rise to Tau. Exon 1 is part of the promoter and Exon 14 is found in the messenger RNA, both are transcribed but not translated (Andreadis et al. 1992)·(Buée et al. 2000).

Like all proteins, Tau has a known Primary structure. It is considered an intrinsically unstructured protein. The primary structure contains 441 amino acids including a high proportion of phosphorylatable amino acids (serine and threonine) (Goedert et al. 1989). Most of the threonine residues reside in the N-terminal region of Tau (Avila et al. 2016). The existence of a secondary structure of Tau has been contentious in the field as Tau is soluble, highly heat-stable, and disorganized in solution (Barré and Eliezer 2013). There have been several renderings of the secondary structure with X-ray crystallography and cryo-electron microscopy. Most conclude it is comprised of α-helices, β-pleated sheets, and a poly-proline double helix bound by transient hydrophobic interactions (Dan and Chen 2019)(Cleveland et al. 1977). Due to the transient nature of the residues in Tau, there is a tertiary structure. The quaternary structure is very chaperoned, due to the formation of an alpha tubulin heterodimer which is an extremely regulated process and involves a lateral and longitudinal interaction with Tau (Serna and Zabala 2001). As previously mentioned, the structure and function of MAPT are highly regulated and chaperoned. It's

the post-translational modifications that lead to deleterious Tauopathy. In healthy cells, Tau aids intercellular movement by directing microtubule mechanisms like kinesin, and dynein (Siahaan et al. 2022). In AD acetylated Tau gradually kills cells by decreasing neuronal synaptic plasticity (Tracy et al. 2016). Hyperphosphorylated Tau causes microtubule dissociation. Hyperphosphorylation also promotes Tau polymerization, and misfolding of Tau, leading to NFTs and changes in subcellular localization of Tau (Gong and Iqbal 2008).

The functions of Tau are vast, and this review just begins to discuss a few of the many facets and functions of the protein *(Figure 2)*. Several biochemists devote their whole lives to unraveling the complexities of Tau. Tau has several mechanisms when it is post-translational modified. Tau is easily phosphorylated, but glycosylation, glycation, deamidation, isomerization, nitration, methylation, ubiquitylation, sumoylation, and truncation also occur (Martin et al. 2011). Tau seeding can also signal apoptosis. While the stabilizing tubulin components of Tau can enable intercellular transport (Wooten et al. 2005). In AD, microglia are the only cells known to phagocytose Tau, but they have been shown to engulf full-length and oligomeric Tau (Das et al. 2020).

In individuals with non-AD pathology, soluble Tau is present in a neuron's extracellular matrix in a monomeric form. Under AD conditions, extracellular hyperphosphorylated Tau can start to aggregate in the brain's interstitial fluid (Yamada et al. 2011). The extracellular Tau will have a pleiotropic effect on neighboring cells and enable the seeding of oligomers (Wu et al. 2016). In culture, Tau was heavily seed-competent, and aggregates formed easily when seeded (Iba et al. 2013). It has been established that Tauopathy is cytotoxic but does not have to enter the cell to cause cellular death. Tau can activate microglia by stimulating their toll-like receptor to activate the inflammasome, causing them to phagocytize live neurons (Pampuscenko et al. 2023).

Tau also has a known master regulator, Low-density lipoprotein receptor-related protein 1 (LRP1)(Rauch et al. 2020). This receptor helps Tau spread to naïve cells and aids its aggregations extracellularly(Rauch et al. 2020). Heparan sulfate proteoglycans (HSPGs) have been shown to work contemporaneously with LRP1(Song et al. 2022). HSPG is a dynamic cell surface receptor with high

endocytic properties that utilizes caveolin-meditated endocytosis and micropinocytosis to enable the extracellular Tau to internalize (Christianson and Belting 2014)·(Wittrup et al. 2009). Due to the highly dynamic nature of the receptor, the route of endocytosis can vary based on how Tau binds because HS has so many repeats in its polymer it can be conjugated easily onto a variety of proteins including Tau (Uhrig et al. 2012). This fusion of Tau to HSPG and its co-receptors signals the downstream MEK/ERK pathway necessary for membrane invagination of Tau, or micropinocytosis (Song et al. 2022). Tau deposition and internalization of Aβ independently are known to activate the MEK/ERK pathway (Lachén-Montes et al. 2016)·(Ferrer et al. 2006). Together in AD, they ensure the pathway is activated. Monomeric Tau relies on clathrin-mediated endocytosis (CME) this process is actin-independent and dynamin-dependent(Evans et al. 2018). This process is most efficient for monomers but not exclusionary. Another endocytic mechanism is lipid raft-dependent endocytosis. This route is defined by its absence of Clathrin, dynamin, and depletion of cholesterol. This is the primary route of uptake for monomeric Tau (Zhao et al. 2021). Some consider HSPGs because they also don't depend on clathrin, but HSPGs are most efficient for Tau oligomers to disrupt cell membranes (Flach et al. 2012) The last method of endocytosis creates tunneling nanotubes (TNTs). The TNTs create cell-to-cell transfer by using actin to transport fractions of the plasma membrane of one cell to another bidirectionally (Tardivel et al. 2016). Being actin-mediated the nanotubes are easily able to be redirected by Tau, and restructured to other proteins like NFT (Sowinski et al. 2008)·(Gousset et al. 2009). The proteotoxicity of Tau heavily contributes to the synaptic dysfunction in AD that leads to cognitive decline. Post-translational modifications of Tau also contribute to its aggregation and obstruction of clearance leading to this toxicity (Tracy et al. 2016). Unfolded native Tau often doesn't aggregate but it does have a higher likelihood of phosphorylating (Wang and Mandelkow 2016).

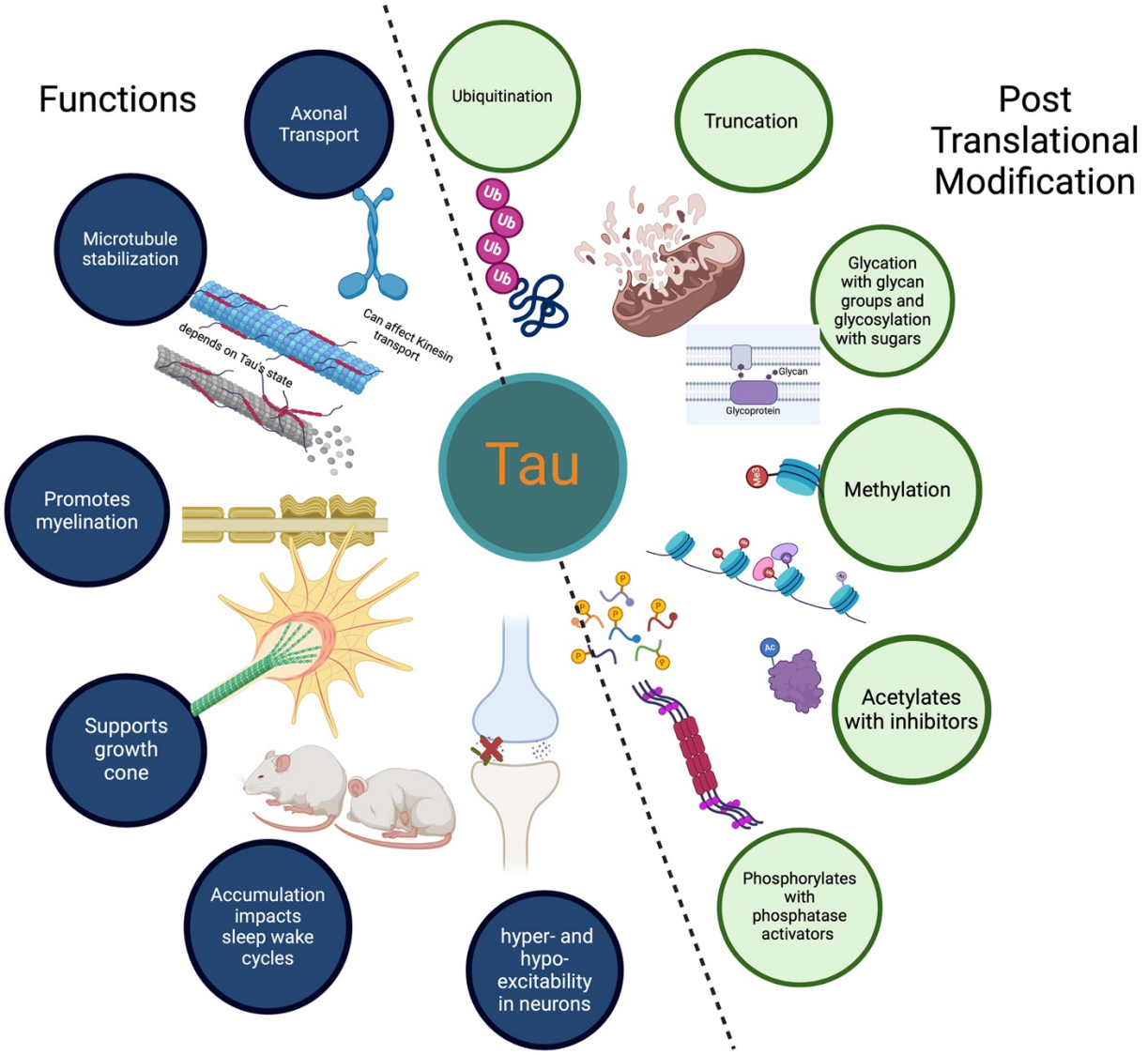

Figure 2: A preview of the functions and Post-Translational Modifications of Tau. Ubiquitination, methylation, acetylation, phosphorylation, glycosylation, glycation, and truncation are a few of Tau's many post-translational modifications possible (green circles to the right of the dashed line). Tau has many functions as depicted in the blue circles left of the dashed line. BioRender was used to generate this figure

CHAPTER 4: ***Amyloid beta***

Amyloid beta comes from the APP protein. Three major APP isoforms in the brain have between 365 -770 amino acids; Aß has between 40-42 amino acids (Mills and Reiner 1999). APP is a transmembrane peptide, and the production begins with mature APP getting cleaved by the β- and γ-secretase in succession. Aß like Tau is also thought to be intrinsically unstructured, but $Aß_{40}$ showed a significant secondary and tertiary structure via NMR (Lührs et al. 2005). Aß fibrils also have a ß-helix-pleated sheet structure. Mouse models have helped shape the structural work in Aß (Kreutzer et al. 2016). Amyloid precursor protein (APP) is caused by the formation of neural plaques comprised of the Aß fragment. These fragments are produced from the cleavage of APP by ß-secretase (Vassar et al. 2009). Other enzymes can act on APP, like α-secretase (TACE), and out-compete ß-secretase for proteolysis of APP when up-regulated(Allinson et al. 2003). As APP is subject to more than one proteolytic pathway there are two splices needed to release an amyloidogenic protein. If α - and γ-secretases were used to cleave APP there could be less deleterious outcomes for an α-secretase product, sAPPα. It was also reported that the fibrilization pathways of Aß mediate its antimicrobial properties. When viral, fungal, or bacterial infections are present Aß depositions increase and the spread of infection decreases (Eimer et al. 2018). In non-pathologic conditions Aß is believed to play a beneficial role in synaptic function and plasticity, contributing to learning and memory processes (Brothers et al. 2018). Aβ may have a neuroprotective role, including the modulation of cholesterol transport and protection against oxidative stress under normal conditions (Giuffrida et al. 2009).

In AD, there is an imbalance between the production and clearance of Aβ, leading to its accumulation and aggregation into extracellular amyloid plaques (Qosa et al. 2014). These plaques are a hallmark of AD pathology. Aβ aggregates activate microglia and astrocytes, leading to a chronic inflammatory response that exacerbates neuronal damage and contributes to the neurodegenerative process. Dysregulated AMPA receptors in AD can also contribute to dysregulated longer potentiation and long-term depression (Jaye et al. 2024).

CHAPTER 5: *Mouse Models of AD*

There are over 200 AD models, most of which are transgenic mouse models. These cutting-edge mice can be developed in several different ways. First desired gene sequences can be microinjected into the pronuclei of a donor-fertilized mouse embryo. Secondly Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR), which utilizes a guide RNA to bind to Cas9. Cas9 is the enzyme that cleaves the DNA of interest at the target site and allows the insertion of an alternative sequence using the cell's endogenous repair mechanisms (Jinek et al. 2012). One example has been the generation of the APOE 3 and APOE 4 knock-ins. The Cas9 complex recognizes the target site on the endogenous mouse APOE gene via the protospacer adjacent motif (PAM). A guide RNA directs PAM and Cas9 to cleave the gene of interest leading to a double-stranded break (DSB). The DSB uses homologous-directed repair (HDR) to allow the insertion of new genes which would be a knock-in or a segment of DNA. To create APOE knock-in mice, mouse exons 2, 3, and most of exon 4 get replaced by human APOE4 sequence including exons 2, 3, 4, and a portion of the 3' UTR sequence by homologous recombination. The other outcome could be a non-homologous repair pathway (NHEJ). In this case, the genes of interest are transcribed but non-functional. This repair pathway often results in insertions and deletions (Jinek et al. 2012). The HDR is knocked into the fertilized eggs of a mouse. Pups are sequenced via PCR and bred to continue the genotype of interest. CRISPR is not without drawbacks. The transcription of a virus is impossible with CRISPR as they cannot repair the damage sustained from the process of transcription (Barrangou et al. 2007)

5.1: Knock-in of APOE and APOE4

Commercially available humanized APOE3 and APOE4 knock-in mice were generated on C57BL/6J background. APOE4 mice primarily display a decrease in dendritic spine density in the amygdala and entorhinal cortex. This effect has been recently shown to be reduced by NSAIDs like ibuprofen. This phenotype is virtually nonexistent in APOE2 and APOE3. APOE knock-in mice are rarely used behaviorally, more commonly their APOE3 and APOE4 knockout counterparts are examined. However, a foundational paper for the APOE knock-in characterized behavior for both APOE 3 and 4

mice comparing and contrasting behavioral phenotypes for both of these alleles. This study looked at the long-term effects of the genetic risk factor over time and how it impacted cognitive decline. They observed cognitive, behavioral, and physiological measurements for 25 weeks (Speidell et al. 2019). To measure mouse spatial learning and memory, they used the Barnes maze and found a significant difference between APOE allele genotypes. The APOE4 mice had a statistically significant decrease in spatial learning. The APOE3 mice had higher PI which did not affect their final performance (Speidell et al. 2019). Of the few studies published, most select a gender and then examine APOE 4 and APOE3 at different ages. This makes the research incomparable. This makes it hard to determine if the age-dependent cognitive decline is due to fluctuations in hormones or sex hormones or receptors(Grootendorst et al. 2005). The one consistent trend most studies have shown is females tend to increase avoidant behavior across all APOE genotypes(Grootendorst et al. 2005; McLean et al. 2022). There is a directly proportional relationship between age and Aβ production in APOE4 mice. This can be observed from circulating plasma levels (Koriath et al. 2019). In contrast, APOE2 and APOE3 have been shown to have less $A\beta_{42}$ circulating(Sharman et al. 2010). The increase in Aβ levels is not sufficient to induce AD-like pathology. Although APOE4 alone is sufficient to induce AD in humans it is necessary but not sufficient in mice(Sepulveda et al. 2022). Although the changes between APOE 2 and APOE 3 cohorts are detectable statistically, they don't result in substantial visual, pathological, or physiological differences. It was suggested to raise the N to an extremely high value so the study would be more adequately powered. This alternative may enable studies to examine more nuanced differences within sample groups of the animal model. This need to have an extremely high N is likely why most studies have chosen to cross these knock-in mutations with an amyloidosis or Tauopathy model that better recapitulates AD. While knock-in mice that don't display Tauopathy wouldn't be the first mouse I chose to emulate AD, it is a great place to start as it's a major risk allele for human disease. The knock-in enables researchers to cross one risk variant gene with other humanized variants that are in other backgrounds more easily, like the triggering receptor expressed on myeloid cells 2 (TREM2).

5.2: Overexpression of Mutated Human Tau P301L

Another common method for producing a mouse model also requires the creation of a gene mutation associated with human disease. Some of the disease models are accomplished by overexpression of human Tau(Iannucci et al. 2020). This is specifically seen with a mutation at the Proline 301 site. One example is the rTg4610 mouse model. When human Tau is mutated ($hTau^{P301L}$) and overexpressed, there is 13 times more protein expression in the mice than endogenous Tau in the rTg4510 mice than there normally would be in a C57BL/6J mouse(Ramsden et al. 2005). Similarly to CRISPR once the gene that is being overexpressed, in this case, P301L, is generated it can be microinjected into the pronuclei of a donor-fertilized embryo of a 129S6 or FVB/N mouse(Ramsden et al. 2005). To generate this overexpression in a regulated manner, the 4510 responder mice that carry the cDNA of human $MAPT^{P301L}$ are crossed with a tetracycline operon-responsive element (TRE) to the activator line that expresses a tetracycline-controlled transactivator (tTa) under a CaMKIIα promoter(Gamache et al. 2019). The transgene can be inhibited by doxycycline and restricted to the forebrain by the CaMKIIα promoter.(Gamache et al. 2019) This fast-developing model can show pathology as early as 2.5 months. Soluble and insoluble Tau is visible in histology, and staining intensifies as Tau filaments deposit. Neuronal degeneration progresses over time (Ficulle et al. 2022). Similar to their human counterparts, the females show more impairment than males, but both have cognitive deficits at 2.5 months(Yue et al. 2011). Spatial memory, contextual fear conditioning, and neural activation continue to decline with age while the Tau burden increases (Cook et al. 2014). Another behavioral phenotype that begins early is hyperactivity. This activity onsets in females at 2 months, and in males at 4-6 months and persists until death (Blackmore et al. 2017). Neuronal deficits start as early as 5 months with alterations in neuronal firing patterns that lead to synaptic instability that can turn into pre-degenerative disease states (Jackson et al. 2017). Vast and progressive neuronal death is visible as forebrain atrophy at 7 months (Gamache et al. 2019). By 8 months, 30 percent of dendritic spine density was lost, but the presence of Tau aggregates did not increase this loss (Kopeikina et al. 2013). Tg4510 mice have severe neuronal atrophy and weight loss by 10 months and a 12-month lifespan. They are a fast model but not the most clinically relevant as they

live significantly less time than a control C57BL/6J (Joly-Amado et al. 2016).

5.3: ***Transgenic Model of P301S***

The mutation in the case of PS19 mice is a Proline to Serine substitution at amino acid 301 of Tau (Lossos et al. 2003).The P301S site is mutated by using the cDNA of the wild-type human T34 isoform Tau (1N4R), the transcript for both mouse and human isoforms consists of exons 1 to 13 excluding exon 3. This transgene is driven by mouse prion promoter (MoPrPr) (Yoshiyama et al. 2007),(Borchelt et al. 1996). The promotor dramatically upregulates human Tau expression in comparison to endogenous mouse Tau. To ensure this transgene is ubiquitously and repeatedly expressed, the use of microinjections of the vector into the germinal vesicle of the fertilized mouse is commonly performed into a B6C3F1/J background (Macdonald et al. 2019). Usually, 10-20 percent of the pups will carry the new gene at birth while the other littermates are genotypically wildtype(National Research Council (US) 1994). When the transgene is expressed, the mice will start to display NFTs, and cortical and hippocampal atrophy at 9 months. The mice will develop and accumulate Tau as early as 3 months and continue through death (Ahmad et al. 2021). They will also have a large reduction in branching basal dendrites in CA1 pyramidal neurons at 3 months which does not progress (Cao et al. 2023). Their levels of bilateral p-Tau staining are symmetrical in the pons, medulla, cerebellum, and hypothalamus from birth to 6 months. Differences in NFTs become more pronounced between 9 and 10 months (Ramirez et al. 2023). The behavioral hyperactivity that was first visible at 6 months quickly dissipates by 9 months as pathological Tau increases and motor strength decreases. At 9 months mice also display a decline in physical condition as seen by lower body weight, lower body temperature, and reduced locomotor activity due to decreased motor strength (Patel et al. 2022). Morbidity is most common at 12 months accompanied by prominent neuronal death, gliosis, and brain atrophy starting at 9 months (Takashima et al. 2023),(Yoshiyama et al. 2007). The short time scale of disease progression is quite rapid in a mouse life cycle, but the seeding of Tau is very efficient in this model making it one of the more pathologically relevant models. Another physiological benefit of the PS19 mice is that they seed pathologic Tau in the hippocampus and cortical regions and display neuronal loss. The mice also display ventricular

enlargement, a classical hallmark of AD (Largo-Barrientos et al. 2021).

PS19 mice are great pathologically and clinically relevant model as they rapidly recapitulate neurodegeneration and BPSD in an animal model. They do this by displaying agitation via hyperactivity, and neurodegeneration via gradual Tau seeding. The downside is neurodegeneration begins early and rapidly progresses without a linear relationship between the symptomology and pathology. Sun et al report that PS19 mice do not display significant s spatial and learning memory deficits, but the mice increase exploratory activity between 9- 12 months (Sun et al. 2020). In contrast, deficits in Y-maze between ages 2 and 12 months in comparison to their wild-type age match controls can be seen. The physiological and functional deficits are not directly correlated. This implies their decline is independent of the presence of one deficiency (Patel et al. 2022). It was found that PS19 mice can learn procedural learning tasks, like the Morris water maze, but struggle with path integration which makes spatial learning harder (Takashima et al. 2023). They have spatial learning and working memory capabilities but impaired path integration. AD patients also have integration dysregulation. PS19 mice also model the BPSD deficits like wandering and sundowning in AD. These animals make studying disease pathology and symptomology more clinically relevant and help researchers understand the genomic implications of disease on a shortened timeline.

Many models of AD have been criticized and fall short of recapitulating the disease due to their closer emulation of FTD. This is a common complaint of the rTG4510 model and has been stated about other MAPT mutant mice. Another complaint about the model is they don't recapitulate AD well. Many therapeutic agents significantly improve and, can even eliminate the phenotype of the mice by genetically interfering with the transgene and not the drug target(Gamache et al. 2019). Seeing a gap in knowledge in the field, and to ensure true Tau seeding our lab uses APP + PS mice that we overexpress with P301L. The transgenic mouse carries two transgenes one for the Swedish mutations (K670N/M671L) and M146L mutation in PS1, together these mutations lead to elevated levels of Aβx-42(Gordon et al. 2002). We then use a tertiary hit to add AAV full-length (4N2R) $TauP^{301}$ retro-orbitally. This method showed Tau seeding and clinically relevant Aβx-42 onset.

CHAPTER 6: *Cellular senescence*

As aging and time are the largest risk factors for Alzheimer's disease and the main inducer of cellular senescence it is imperative to determine the interconnectivity between the two scientific phenomena(Hou et al. 2019)·(McHugh and Gil 2018). Determining the underpinnings of cellular senescence and its effect on the pathology of Alzheimer's helps define what mechanistic agents are involved in the cognitive decline in AD. It helps clarify what cell types are senescent in the context of diseased aging (Dehkordi et al. 2021). This research contextualizes how Alzheimer's disease places differing physiological stresses on cells. It shows how these stresses can induce senescence and physiological changes that could lead to cognitive decline atypical of normal aging, which can be paramount in facilitating therapeutic treatment (Lyons and Bartolomucci 2020). In this context physiological stress does not have to be sheer physical stress it could be anything chronic that perturbs the cell or dysregulates it.

Many AD-associated pathologies have been linked to contributing senescent factors or inducers (Musi et al. 2018). For example, NFTs are associated with the induction of senescence and cognitive decline (Musi et al. 2018). Some studies find senescent cells in AD models (Liu 2022). The field lacks a bridge that connects and synthesizes the knowledge in the senescence field, AD field, and what's known about amyloid beta, Tau, inflammation, and stress. If collectively and contextually these pieces were examined the picture might elucidate more specific mechanistic avenues to investigate cell type-specific senescence induction in AD (Gillispie et al. 2021). This is why our lab uses a multidisciplinary approach when investigating cell senescence in the context of AD. The Gordon lab examines disease from a behavioral perspective, using multiple tests in vivo, pathologically via immunohistochemistry and, molecularly doing flow cytometry or PCR. These approaches will elucidate the process of cellular senescence in microglia on a proteomic, and transcriptomic level.

Cellular senescence is the process where cells age, and stop dividing but do not die under stress (Wiley and Campisi 2021). Cell division and replication lead to their Hayflick limit (Hayflick 1965). This limit is considered where telomere begins to shorten in the cell cycle and correspond with the cell's replication cycle or passage number to help identify aging and division (Verma et al. 2020). This DNA is

degraded with each replication progressed until the integrity of the DNA is no longer maintained inducing cell death. This makes DNA degradation a hallmark of cellular senescence (Harley et al. 1990). Senescence is a programmed, instructive process in the cell cycle that is a critical mediator of apoptosis and macrophage-mediated clearance of debris (Storer et al. 2013).

The cell cycle has four phases: first gap phase (G1), synthesis phase (S), second gap phase (G2), and mitotic phase (M). The amount of time a cell spends on each phase differs from cell type to cell type (Abou Chakra et al. 2021). There are several opportunities for interjection in the cycle that can induce permeant cell cycle arrest. These interjections cause phenotypic and metabolic changes in cells that are irreversible (Wiley and Campisi 2021). These interjections into the cell cycle are intended to stop and continue stopping cell growth in an anti-proliferative manner (Campisi et al. 2011; Campisi 2013). Two anti-proliferator pathways are used to halt growth: p53 and p16/Rb. The cell cycle interjections utilized include five mechanisms to stop proliferation: Production of reactive oxygen species (ROS), DNA damage, Mitochondrial dysfunction, Oncogenic stress, and Production and activation of senescent-associated secretory phenotype proteins (SASPs)(Sanders et al. 2013). These interjections impact every aspect of the cell cycle.

The interaction of Cyclin D with Cyclin-dependent kinase 4/6 (CDK4/6) and CDK 2 complexes leads to induced arrest at G1 phase. In S phase CDK4/6 will lead to phosphorylation of retinoblastoma (pRb) tumor repressor which can also induce senescence via ROS (Dulić et al. 1993). Dysregulation of the CDK2 complex will lead to DNA damage (Liu et al. 2020). This DNA damage induces a senescence phenotype at G1 phase and S phase. Similar induction of senescence occurs from DNA damage from the ATM/P53/P21 pathway. The short telomeres break and lead to a DNA damage response (DDR) which, blocks the G1 to S phase (d'Adda di Fagagna et al. 2003). The last chance to arrest is G2 phase interjections. These are checkpoint signals that check for DNA double-stranded breaks preceding the G2 to Mitotic phase transition(Abraham 2001). Due to telomere shortening the DNA will not pass checkpoints like P21 an upstream regulator of the G2 (Smits et al. 2000). (Figure 3.)

The utility of these proteins has been mentioned but their function has not been described in

depth. P53 is a tumor suppressor protein whose primary function is to regulate cell growth and division and its primary job is to regulate proliferation(Wang et al. 2023a). It does this through an extensive network of post-translational modifications including ubiquitination, acetylation, methylation, and phosphorylation. The post-translational modifications are induced by stress, hypoxia, nutrient deprivation, or cancer (DeHart et al. 2014). P53 has a primary role in senescence inhibiting CDKs and cyclin b but it can also induce apoptotic pathways if needed

(Taylor and Stark 2001). P21 is a cyclin-dependent kinase inhibitor 1 also known as $p21^{Waf}$. Its main role is to bind to CDK complexes and inhibit CDK2. P21 also helps determine P53 dynamics and DNA damage levels to induce proliferative senescence (Hsu et al. 2019).

The cell cycle arrest uses the expression of P21, P53, and SASP to signal neighboring cells to induce senescence and signal resident immune cells to target senescent cells as antigen-presenting cells (Rovillain et al. 2011)·(Salminen et al. 2012). The role of P16 in the cell is to stabilize the cell during the arrest process; the gene is not sufficient to induce senescence (Stein et al. 1999). The full name of p16 is P16NK4a. The gene is composed of 3 exons. With the use of an alternative start site and an alternative reading frame, a second protein is generated from the same gene, p14Arf (Serrano et al. 1993). P16 is a great marker for the induction of senescent cells because P16 is an upstream modulator of pRB and interacts with p53 (Parry et al. 1995)·(Collins and Sedivy 2003).

The mechanism of initiating cellular senescence in vivo would look like normal aging, physical stress, environmental stress, or a wound and injury (Tchkonia and Kirkland 2018) *(Figure 3).* The aforementioned activities can initiate senescence which starts the processes of stressed-induced reactive oxygen species (ROS), apoptosis, or protein turnover (Liguori et al. 2018). It is unknown if there is a synergistic mechanism that utilizes all of the initiation mechanisms to help induce senescence or if only one key criterion is needed in a threshold amount. Once senescence is induced it is an irreversible proliferative arrest phase and is measurable by markers like P16 and other senescence-associated secretory phenotypes (SASPs)(Calcinotto et al. 2019). Pathophysiologically in AD, this would look like a pro-inflammatory pathway in patients. That pathway targets cancer cell oncogenes, tumor

microenvironments, and autoimmune diseases, it is chronically active (Malaquin et al. 2019)

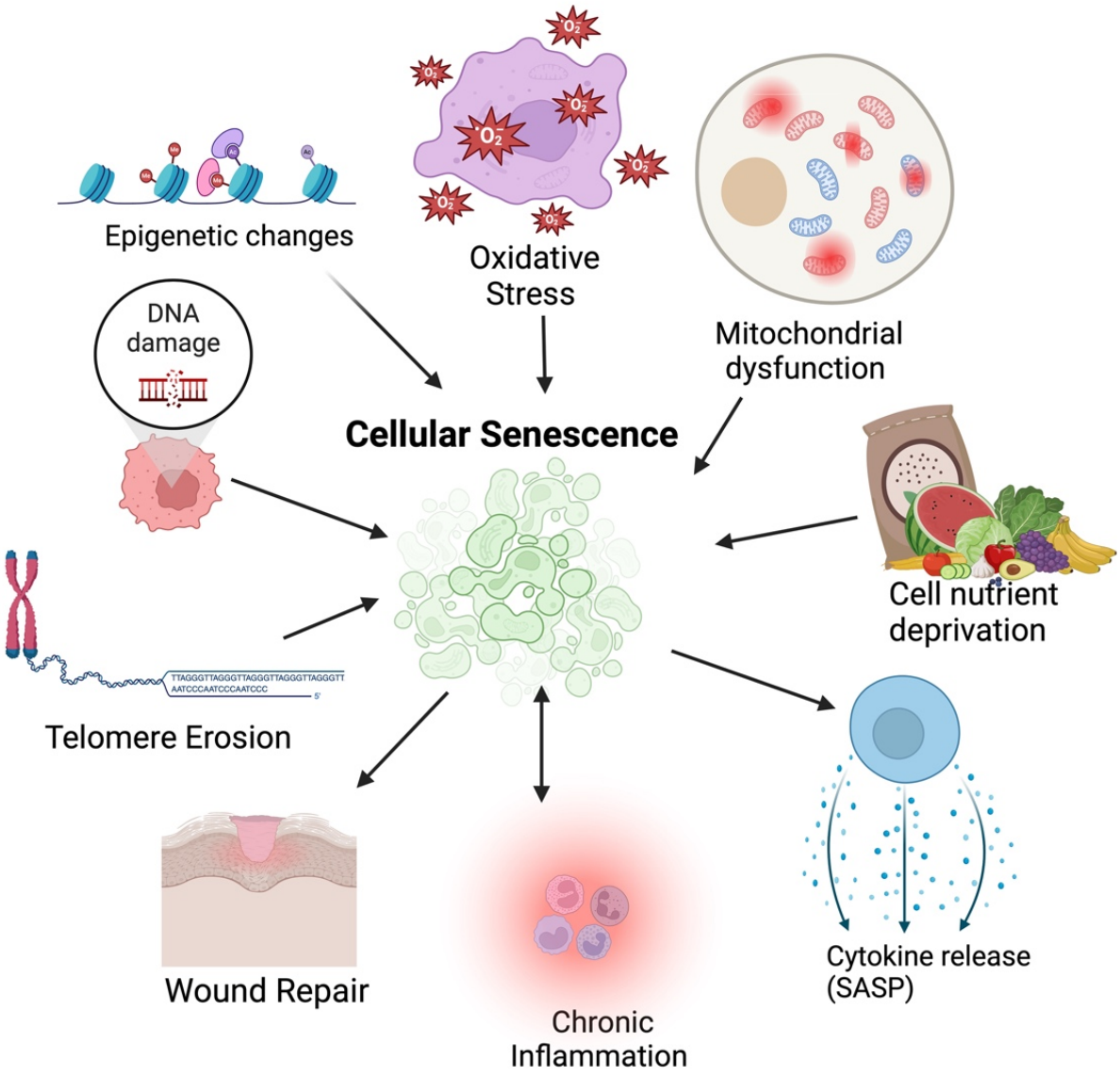

Figure 3: Inducers and responses of cellular senescence. Epigenetic changes like methylation, histone modification, and chromatin remodeling contribute to age-related cellular senescence (Wang et al. 2022). Other cellular stressors resulting in senescence include telomere shortening, oxidative stress, mitochondrial dysfunction, and nutrient deprivation. Factors contributing to senescence induction are indicated with black arrows leading toward senescence. Cellular responses resulting from senescence include wound repair, inflammation, and SASP response as indicated by black arrows pointing away from senescent cells. Figure generated with BioRender.

CHAPTER 7: *TWAS*

Several molecular tools are at researchers' disposal for modern molecular analysis of disease pathology; one popular technique employed is Genome-Wide Association studies (GWAS). GWAS examines an organism's whole genome, takes a system-wide analysis, makes associations of genes, and tries to pull out genes of interest from the association (Uffelmann et al. 2021). This process gives insight into the trait variations within gene associations and helps understand the functions of gene linkages (Slatkin 2008). GWAS in AD requires the collection and use of DNA. From individuals experiencing phenotypic AD, GWAS requires large sample sizes to achieve reproducible data with significant associations (Marek et al. 2022). The post-hoc analysis of GWAS is transcriptome-wide association studies (TWAS). TWAS studies can examine genes from a single tissue, an organ, or a subset from the related GWAS study. TWAS only utilizes genomic sequences like RNA. These studies aim to prioritize genes and traits within a singular study by their single nucleotide polymorphisms (SNPs) from GWAS studies (Li and Ritchie 2021). TWAS is highly popularized due to its ability to find a causal link in associations between genes and strength in gene associations. TWAS also created a stronger prioritization ranking system of genes of interest (Wainberg et al. 2019).

TWAS has been a helpful agent to delve into the underpinnings of microglia relationships with AD and how immunology and inflammation are interconnected with immunoreactivity in neurodegeneration. To help understand the subcategories of microglia researchers had to understand microglia activation. This process is highly regulated through CX3CR1-CX3CL1, SIRPa-CD47, and other checkpoint inhibitors (Hanisch and Kettenmann 2007). The dynamics between molecular signatures in genetic markers in several subcategories of microglia states are significantly influenced by age (Fujita et al. 2024). This is implicated in controlling microglia phenotypic differentiation and activation mechanisms (Sun et al. 2023). From here TWAS can pull transcripts of interest and make the best associations once the mechanism of pathology is determined. Almost weekly new TWAS studies pull and validate new genes of interest from microglial associations.

CHAPTER 8: *Historical Microglial Subtypes*

Microglia were viewed as having three distinctive subtypes: M0 (resting state), M1, and M2, which act as a dipole state. M1 and M2 microglia can work in several mechanisms (Guo et al. 2022)(Block et al. 2007). The nomenclature of microglia has been contentious since the mid-1920s (Tremblay et al. 2015). The use of transcriptomics has provided insight into the functions of microglia but also left knowledge gaps with the current nomenclature (Ransohoff 2016). The completeness of the nomenclature has been a point of contention, but the validity of the historical subtypes has been affirmed and expanded (Wang et al. , 2023b).

Historically M1 microglia act as injury and infection responses by promoting the destruction of pathogens (Horwitz et al. 2008). M1 microglia exist in a pro-inflammatory state, releasing proinflammatory cytokines and ROS (Taylor and Stark 2001; Butturini et al. 2019) They can work in conjunction with other macromolecules like cytokines, ROS, and proteases in a process called classical activation. This process of regulating this cascade is investigated through epigenetics and genetic markers such as Jmjd3, a histone H3K27me3 demethylase Jumonji domain (Tang et al. 2014)(Scholz et al. 2024). The other form of activation is called alternative activation and occurs in M2 microglia when an anti-inflammatory cytokine is added to bring the glia back to a resting state(Block et al. 2007). M2 can also repair cells and are involved in wound healing (Umpierre and Wu 2021).The M1 microglia are typically seen as destructive but also present markers of M2 microglia (Martinez and Gordon 2014). The nomenclature leaves many gaps and lots of ambiguity within the field of microglial research. The complexity and expansiveness of their capacity beyond the limited markers and polarity lead to the exploration of further effector functions.

CHAPTER 9: *DAMS and HAMS*

Disease-associated Microglia (DAMs) were found by examining mouse microglial genes during single-cell RNA sequencing. DAMs are based on cluster-specific expression patterns of the most variable 500 genes (Keren-Shaul et al. 2017). When DAMSs were originally defined in the mouse model of AD they were defined as phagocytic TREM 2 independent and dependent cells (Keren-Shaul et al. 2017). DAMs show increased expression of genes such as *APOE, Ctsd, Lpl, Tyrobp, and Trem2* (Lambert et al. 2013). DAMS also encode a large number of known risk factors for AD (Deczkowska et al. 2018). In contrast, homeostatic microglial genes (*P2ry12, P2ry13, Cx3cr1*, and *Tmem119*) were reduced.

Human Associated Microglia (HAMs) were first defined as human-associated microglia signatures in AD mouse brains. The most successful implementation to note was xenografting human AD microglia from disease-associated tissue into APP knock-in mice and performing transcriptomics on the glia (Mancuso et al. 2024). There are 57 core genes conserved between human and mouse microglia. These genes maintain effector function and adapt to environmental changes (Abels et al. 2021) . Transcriptomics can identify many risk factors and help narrow crucial gene loci.

In a TWAS cohort of 115 people presenting with AD, it was found that there were no differently expressed microglial genes between males and females. Within this cohort, they were able to identify a subset of microglia genes that varied in cortical regions and contributed to age (Srinivasan et al. 2020). When looking at TWAS that examined *CCL3, IL1B, IL15, IL4R, IL17R*, and *IL10RA* expression, they found functional enrichment in three inflammatory states in microglia including immune responses and cytokine pathways (Sun et al. 2023). *IL15,* a protein cytokine, and genes *MS4A6A*, *MS4A4A*, *NME8*, and *GPR141* were thought to contribute toward elevated microglial-based AD pathology due to HAMs (Srinivasan et al. 2020). It was found that HAMs have no TWAS associations with disease-associated microglia DAMs (Srinivasan et al. 2020).

CONCLUSION

Depending on the pathology and symptomology several techniques can be implored to exemplify disease in a rodent model. Mouse models are crucial in Alzheimer's disease research, providing invaluable insights into the disease's mechanisms and enabling the development and testing of potential therapies. Several investigatory techniques such as CRISPR, GWAS, and TWAS were discussed in this review. The goal was to understand how to use these techniques going forward to investigate the role of senescent microglia during their aging and development under AD conditions. Cellular senescence, plays a dual role in aging and disease, acting both as a barrier to cancer and a contributor to tissue degeneration and age-related pathologies. Microglia activation is crucial for the central nervous system's immune defense and neural homeostasis. Activated microglia can either protect and repair neural tissue or contribute to neuroinflammation and degeneration. Understanding and modulating microglial responses is key to developing therapies for neurological disorders like Alzheimer's and Parkinson's disease. Our goal is to understand the impact of age on the immune system in a diseased state to identify further where to mediate neuroprotection and reduce chronic inflammation. This gives the best chances of improving patient outcomes.

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