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Exploring Alzheimer's Disease Pathogenesis and Modern Therapeutic Approaches Using *C. elegans Model*: A Comprehensive Review

Divyata Desai[1], Kundan Kumar Mishra[2]

[1]Research Scholar, Department of Biotechnology, Genetics & Bioinformatics, Natubhai V. Patel College of Pure & Applied sciences, Charutar Vidya Mandal University, Vallabh Vidyanagar – 388120, Gujarat, India
Email: *divyata[at]nvpas.edu.in*

[2]Assistant Professor, Department of Biotechnology, Genetics & Bioinformatics, Natubhai V. Patel College of Pure & Applied sciences, Charutar Vidya Mandal University, Vallabh Vidyanagar – 388120, Gujarat, India
Email: *kundan[at]nvpas.edu.in*

Abstract: ***Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the accumulation of amyloid - beta (Aβ) plaques, tau tangles, and the eventual death of neurons. Despite extensive research into its mechanisms, existing treatments primarily provide symptomatic relief rather than addressing the underlying causes of the disease. The nematode Caenorhabditis elegans (C. elegans) has emerged as a valuable model organism for investigating AD due to its short life cycle, simple nervous system, and genetic tractability. This review explores how C. elegans models contribute to our understanding of Aβ toxicity, tau pathology, mitochondrial dysfunction, and oxidative stress in AD. Additionally, we examine the utility of C. elegans in drug discovery, discuss the limitations of this model, and highlight future directions for AD research.***

Keywords: Alzheimer's disease (AD), *Caenorhabditis elegans* (*C. elegans*), Amyloid - beta (Aβ) toxicity, Tau pathology, Nervous system, Neuroprotective therapies

1. Introduction

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder globally, currently affecting approximately 6.7 million Americans aged 65 and older (Alzheimer's Association, 2023). It is the leading cause of dementia, characterized by a gradual decline in cognitive functions such as memory, reasoning, and executive functioning. The pathology of AD is primarily defined by two hallmark features: the extracellular deposition of amyloid - beta (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) formed by hyperphosphorylated tau protein (Selkoe & Hardy, 2016). These pathological changes lead to synaptic dysfunction, neuronal death, and ultimately brain atrophy (Serrano - Pozo et al., 2011). Numerous studies have shown that oxidative stress, mitochondrial dysfunction, and impaired proteostasis play central roles in AD pathogenesis (Swerdlow, 2012). Despite advances in our understanding of these mechanisms, current pharmacological treatments—including cholinesterase inhibitors and NMDA receptor antagonists—only alleviate symptoms without modifying disease progression (Cummings et al., 2020). Therefore, alternative models for studying AD mechanisms and discovering novel therapeutics are crucial.

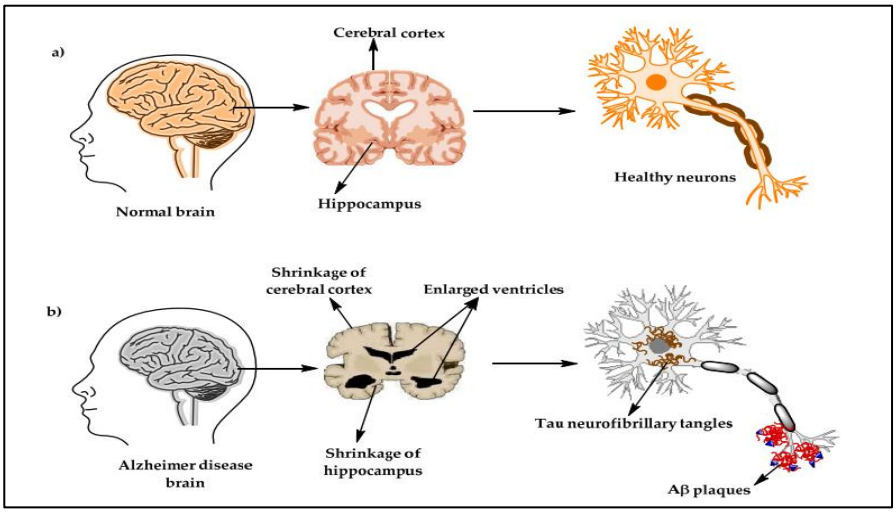

Figure 1: Brain structure a) Healthy brain b) Alzheimer's disease brain (Zenaib Breijyeh & Rafik Karaman 2020)

The nematode *C. elegans* has become a preferred model organism in neurodegenerative disease research due to its simplicity, rapid life cycle (approximately three weeks), and well - mapped nervous system consisting of only 302 neurons (Kaletta & Hengartner, 2006). More than 60% of human disease genes have homologs in *C. elegans*, including those

implicated in AD (Shaye & Greenwald, 2011). Additionally, its small size, transparency, and ease of genetic manipulation enable large - scale genetic screens and in vivo imaging of disease processes (Harrington et al., 2018). In the context of AD research, several *C. elegans* models expressing human Aβ and tau have been developed to study protein aggregation, neurotoxicity, and lifespan effects (Link, 1995). These models have been crucial for high - throughput drug screening and investigating therapeutic strategies (Alexander et al., 2014). Moreover, *C. elegans* has a conserved stress response system that provides insights into oxidative stress and mitochondrial dysfunction in neurodegeneration (Dai et al., 2018).

Pathogenesis of Alzheimer's Disease in *C. elegans*

Amyloid Beta (Aβ) Aggregation

The deposition of Aβ in the brain is one of the earliest pathological features of AD; aggregation of Aβ peptides leads to synaptic loss and neuronal death (Hardy & Higgins, 1992). The *C. elegans* strain CL4176 has been engineered to express human Aβ1 - 42 under a temperature - inducible promoter and has been widely used to model Aβ - induced paralysis and toxicity (Drake et al., 2003). Upon expression of Aβ, these worms exhibit progressive paralysis—an effective readout for studying the molecular underpinnings of Aβ aggregation and its associated neurotoxicity (Fonte et al., 2011). Recent studies using *C. elegans* have highlighted the role of oxidative stress in exacerbating Aβ toxicity. Elevated levels of reactive oxygen species (ROS) and mitochondrial dysfunction contribute to neuronal damage linked to Aβ aggregation in these models (Yee et al., 2014). Compounds such as resveratrol and curcumin have been shown to mitigate Aβ toxicity by reducing ROS levels and promoting proteostasis (Chen et al., 2013; Lim et al., 2021).

Tau Pathology

In addition to Aβ plaques, tau tangles represent a core pathological hallmark of AD. Tau is a microtubule - associated protein that stabilizes neuronal microtubules; however, when hyperphosphorylated, it forms toxic aggregates that lead to neurodegeneration (Ballatore et al., 2007). Models of *C. elegans* expressing human tau—such as the tau (V337M) mutant strain—exhibit tau aggregation alongside impaired motor function (Kraemer et al., 2003). These models have been instrumental in identifying molecular pathways involved in tau toxicity—including those regulating tau phosphorylation, autophagy processes, and proteostasis mechanisms (Tóth et al., 2012). Recent findings indicate that autophagy plays a critical role in mitigating tau - induced toxicity; thus targeting autophagic pathways may provide novel therapeutic avenues for treating AD (Chapman et al., 2019). Additionally, inhibitors targeting tau kinases like GSK - 3β have shown promise in reducing tau phosphorylation and ameliorating neurodegeneration within *C. elegans* models (Kraemer et al., 2006).

Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress and mitochondrial dysfunction are central to AD pathology as they contribute to neuronal energy deficits, synaptic loss, and cell death (Swerdlow, 2012). In *C. elegans*, oxidative stress can be directly assessed using markers for ROS production and mitochondrial activity (Cypser & Johnson, 2002). The CL4176 strain has demonstrated that increased ROS levels accelerate Aβ - induced paralysis—further linking oxidative stress to AD progression (Yee et al., 2014). Studies utilizing mitochondrial - targeted antioxidants like MitoQ have shown promising results in reducing Aβ - induced oxidative damage while improving neuronal health within *C. elegans* models of AD (James et al., 2015). These findings suggest that therapies aimed at addressing mitochondrial dysfunction alongside oxidative stress could offer neuroprotective benefits against AD progression (González - Lafuente et al., 2012).

Genetic Models and Their Contributions

Transgenic *C. elegans* Strains

Various transgenic strains expressing human genes associated with AD have been critical for elucidating molecular mechanisms behind Aβ and tau toxicity. The CL4176 strain allows researchers to investigate genetic pathways involved in Aβ toxicity by providing a clear phenotype indicative of temperature - induced paralysis (Drake et al., 2003). Other transgenic models expressing tau mutants enable studies on tauopathies' effects on neuronal function (Kraemer et al., 2003). These models have identified several key genetic pathways modulating AD pathology; for instance, insulin - like signaling has been shown to influence Aβ aggregation while linking metabolic disorders with increased risk for developing AD (Murphy et al., 2003). Genetic screens conducted using *C. elegans* have revealed important regulators involved in proteostasis maintenance as well as mitochondrial function modulation that contribute significantly toward disease progression (Vabulas & Hartl, 2005).

Gene Function Studies with CRISPR - Cas9

The advent of RNA interference (RNAi) along with CRISPR - Cas9 gene - editing technologies has significantly enhanced our ability to study gene functions within *C. elegans* models related to AD (Shen et al., 2014). RNAi screens systematically knock down specific genes to identify those that influence Aβ toxicity—including heat shock proteins along with other regulators involved in autophagy processes or chaperone activities that maintain protein homeostasis within cells affected by neurodegenerative diseases like Alzheimer's disease (Fonte et al., 2008). CRISPR - Cas9 technology allows precise genetic modifications; researchers have utilized it effectively for creating specific mutations within genes such as APP or PSEN1—facilitating detailed examinations regarding their roles concerning production or aggregation processes involving amyloid precursor proteins implicated within Alzheimer's pathology (Kim et al., 2020). This technology also enables generation of humanized C. elegans models that closely mimic human AD pathology (Sinha et al., 2018).

Drug Screening in *C. elegans*

High - Throughput Drug Screening

The simplicity along with scalability inherent to *C. elegans* makes it an ideal platform for high - throughput drug screening initiatives aimed at identifying compounds capable of reducing either Aβ or tau toxicity effectively. Numerous studies have utilized these models extensively for screening small molecules such as resveratrol, curcumin, and

epigallocatechin gallate (EGCG) —all demonstrating efficacy through delaying paralysis while extending lifespan among transgenic strains expressing amyloid - beta peptide (Wu et al., 2006; Lim et al., 2021). These compounds operate primarily by diminishing levels associated with oxidative stress while enhancing overall proteostasis or promoting autophagic processes within affected neurons (Parker et al., 2012). Recently researchers began *leveraging C. elegans* specifically targeting drugs aimed at addressing both mitochondrial dysfunction alongside oxidative stress linked directly toward Alzheimer's pathology. MitoQ—a mitochondrial - targeted antioxidant—has exhibited effectiveness through reducing reactive oxygen species production induced specifically via amyloid - beta while improving overall neuronal health observed within these experimental settings (James et al., 2015). This underscores potential applications utilizing C. elegans toward identifying novel therapeutics targeting mitochondrial pathways relevant toward combating Alzheimer's disease.

Advantages and Limitations of Using *C. elegans* in Alzheimer's Disease Research

Strengths

C. elegans offers numerous advantages as a model organism for studying Alzheimer's disease:

- **Genetic Manipulation**: The ease with which researchers can manipulate genes allows for targeted studies on specific pathways involved in AD.
- **Rapid Life Cycle**: With a life cycle lasting only about three weeks from egg to adult worm, researchers can quickly generate results.
- **Conserved Biological Pathways**: Many biological processes are conserved between humans and *C. elegans*, making it easier to draw parallels between findings from this model organism and human biology.
- **High - Throughput Capabilities**: The ability to conduct large - scale screenings makes it feasible to test numerous compounds simultaneously.

Limitations

Despite its advantages:

- **Simplistic Nervous System**: The nervous system of *C. elegans*, consisting only of 302 neurons compared to billions in humans, limits the complexity that can be modeled.
- **Differences Between Species**: While many pathways are conserved between humans and worms, significant differences exist that may affect how findings translate into human biology.
- **Lack of Certain Human - Specific Proteins**: Some proteins involved in AD may not be present or function differently in *C. elegans*, which could impact the relevance of certain studies.

Future Directions in *C. elegans* Alzheimer's Disease Research

Emerging Techniques

New techniques such as CRISPR - Cas9 gene editing and optogenetics hold promise for enhancing research capabilities within *C. elegans*. These tools can facilitate precise genetic modifications while allowing real - time manipulation of neuronal activity.

Unexplored Areas

There remains a need for further exploration into tau pathology within *C. elegans*, as well as investigations into novel therapeutic targets that could provide new insights into AD treatment strategies.

2. Conclusion

C. elegans presents substantial advantages for investigating molecular mechanisms underlying Alzheimer's disease—particularly those related specifically toward both Aβ along with tau pathology. Its inherent genetic tractability coupled alongside rapid life cycle facilitates high - throughput drug screening efforts making it an invaluable resource dedicated toward advancing our understanding surrounding this complex disorder. Although certain limitations exist due largely stemming from its simplistic nervous system structure when compared against humans, ongoing advancements involving gene - editing technologies coupled alongside humanized model systems promise expanded utility moving forward into future research endeavors. By capitalizing upon strengths associated with C. elegans, researchers stand poised toward gaining new insights regarding both pathogenesis linked with Alzheimer's disease while simultaneously developing effective therapeutic interventions.

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