Microtubule Dynamics and Neuronal Morphogenesis: A Survey

www.surveyx.cn

Abstract

Microtubule dynamics, post-translational modifications (PTMs), and microtubule-associated proteins (MAPs) are integral to neuronal morphogenesis and have significant implications for neurodegenerative diseases. This survey paper explores the dynamic instability of microtubules, essential for neuronal architecture and intracellular transport, and how disruptions in these dynamics contribute to conditions like Alzheimer's and Parkinson's diseases. PTMs modulate microtubule dynamics by influencing microtubule stability and protein interactions, which are crucial for neuronal differentiation and synaptic connectivity. The role of MAPs in modulating microtubule dynamics during axon guidance is also examined, highlighting their importance in neuronal connectivity and the establishment of neural circuits. The paper emphasizes the need for future research to elucidate the molecular mechanisms of microtubule dynamics, explore the effects of phosphorylation on MAPs, and investigate the regulatory mechanisms optimizing cellular transport. Understanding these complex interactions is vital for developing therapeutic strategies to stabilize microtubules and mitigate neurodegenerative disease progression. The survey underscores the importance of integrating advanced imaging techniques and computational models to enhance our understanding of neurobiology and inform innovative therapeutic approaches.

1 Introduction

1.1 Importance of Microtubule Dynamics

Microtubule dynamics are essential for neuronal morphogenesis, serving as dynamic polymers of -tubulin crucial for intracellular organization and chromosome segregation [1]. The alternating phases of polymerization and depolymerization generate forces necessary for cellular functions, including axonal transport and cell migration, which are vital for developing and maintaining neuronal structures. The regulation of these dynamics is critical for shaping the cerebral cortex's cytoarchitecture and influences the organization and classification of neuronal types [2].

Microtubule-associated proteins (MAPs), such as Tau, MAP2, and MAP4, modulate microtubule stability and dynamics, significantly affecting neurite morphogenesis and neuronal architecture [3]. Their interaction with microtubules is vital for regulating motor transport within cells, emphasizing their importance in neuronal development [4]. Moreover, microtubule dynamics are crucial for growth cone turning, a process essential for axon guidance and synaptic connectivity, forming the basis of functional neuronal networks [5].

In neurobiology, microtubule dynamics are implicated in neurodegenerative diseases, such as Parkinson's disease, underscoring their importance in maintaining neuronal health [6]. Proteins like Cdk5, which influence synaptic plasticity and cognitive functions, further highlight the critical role of microtubule dynamics in neuronal morphogenesis [6]. Understanding these dynamics is vital for elucidating the mechanisms underlying neuronal development and addressing the pathophysiology of neurodegenerative diseases [7].

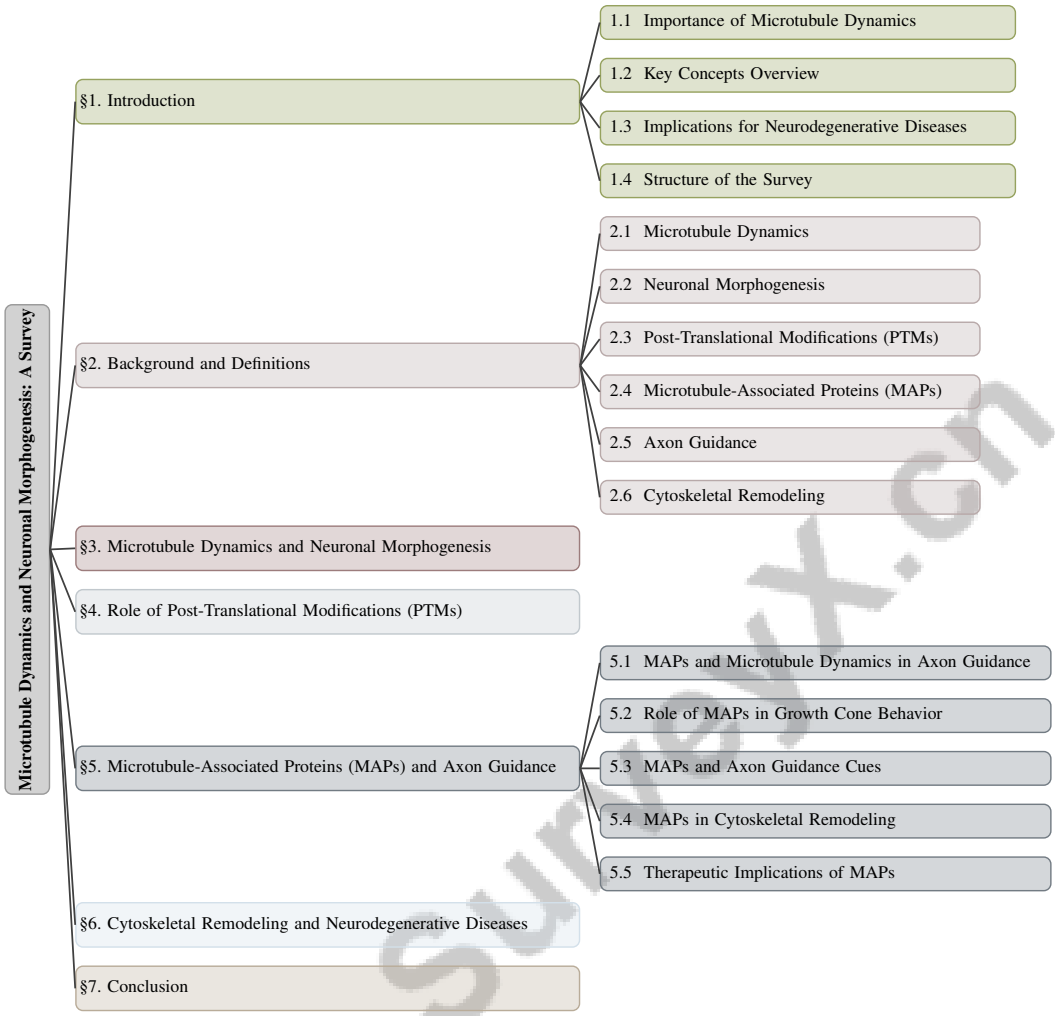

Figure 1: chapter structure

1.2 Key Concepts Overview

Microtubules exhibit dynamic instability, rapidly alternating between polymerization and depolymerization phases, regulated by tubulin availability and length-dependent catastrophe mechanisms [8]. This dynamic nature is fundamental to intracellular transport and mitotic processes [9]. MAPs play a critical role in stabilizing microtubules and modulating their dynamics, impacting neuronal morphogenesis and axon guidance. In mammals, MAPs are linked to various physiological roles and pathologies, emphasizing their importance in cellular function and integrity [10].

Post-Translational Modifications (PTMs) are crucial for regulating protein functions, influencing microtubule dynamics and MAP interactions [11]. These modifications can alter protein activity, localization, and stability, thereby affecting neuronal development and function. Axon guidance, orchestrated by a network of receptors and ligands, is essential for establishing functional neural circuits during development and in response to environmental cues [12].

Cytoskeletal remodeling is vital for maintaining neuronal architecture, influenced by mechanical forces and the cellular environment [13]. This remodeling is critical for structural integrity and adapting to mechanical stress, facilitating effective signal transduction. Additionally, proteome-wide association studies have identified proteins related to cognitive trajectories, providing insights into potential biomarkers for cognitive resilience and their relevance in neurodegenerative diseases [14]. These concepts collectively frame our understanding of the complex processes involved in neuronal development and highlight potential therapeutic targets for neurodegenerative disorders.

AI-generated, for reference only.

1.3 Implications for Neurodegenerative Diseases

Microtubule dynamics are pivotal in understanding neurodegenerative diseases (NDs) like Alzheimer's and Parkinson's, where cytoskeletal integrity disruptions significantly contribute to disease progression [15]. The progressive loss of neurons and protein aggregates, including amyloid-beta and tau, leads to neuronal dysfunction and cognitive decline [16]. The dysregulation of axonal transport, heavily reliant on intact microtubule networks, exacerbates synaptic deficits and neuronal loss in NDs [17], highlighting the urgent need for therapies aimed at stabilizing microtubule dynamics.

PTMs play a crucial role in regulating MAPs and their interactions with microtubules, shedding light on the molecular mechanisms underlying NDs. These modifications influence tau stability and function, a MAP central to tauopathies, leading to microtubule network disruption and neurodegeneration [18]. Innovative therapies, such as photoacoustic stimulation, demonstrate the potential of targeting microtubule dynamics in treating neurodegenerative diseases [19].

Axon guidance molecules (AGMs), including Netrins, Semaphorins, and Ephrins, are crucial in regulating axonal growth and influencing immune responses in the central nervous system [20]. Netrin-1, in particular, is vital for axonal guidance, affecting axon attraction and repulsion, with implications for understanding and potentially treating neurodegenerative diseases [21].

The dynamic instability of microtubules, characterized by growth and shrinkage phases, is essential for neuronal health and is disrupted in NDs [1]. Mechanochemical modeling of microtubule dynamics reveals the importance of conformational changes in microtubule growth, crucial for stabilization and providing insights into cell proliferation and differentiation in normal and pathological conditions [1]. Understanding these complex interactions can lead to more effective strategies to mitigate neurodegenerative diseases and improve patient outcomes.

Cdk5 activity, when deregulated, significantly remodels the neuronal cytoskeleton, contributing to neurodegenerative processes [6]. The propagation and accumulation of toxic proteins in the brain are central to the progression of neurodegenerative diseases, emphasizing the need for a deeper understanding of these processes for potential therapeutic interventions [22]. Addressing the high cost and complexity of experimental methods for detecting PTMs is essential for advancing this field and developing reliable biomarkers and therapeutic interventions for neurodegenerative diseases [23].

1.4 Structure of the Survey

This survey is systematically organized to explore the intricate processes and molecular interactions governing neuronal development, focusing on microtubule dynamics and their implications for neurodegenerative diseases. The introduction emphasizes the critical role of microtubule dynamics in neuronal morphogenesis and their essential functions in neuronal growth, morphology, migration, and polarity. It also discusses the broader implications of these dynamics in neurobiology, particularly concerning neurodegenerative disorders like Parkinson's disease. Additionally, the introduction provides an overview of key concepts, including MAPs like tau, their impact on microtubule stability, the significance of PTMs in regulating microtubule function, and the processes of axon guidance and cytoskeletal remodeling, vital for proper neuronal function and development [24, 8, 9, 1, 25].

Subsequent sections delve into the background and definitions, offering detailed explanations of core concepts involved in the survey, such as microtubule dynamics, neuronal morphogenesis, and their roles in neuronal development and function. The section on microtubule dynamics and neuronal morphogenesis discusses how these dynamics contribute to neuronal structure, emphasizing stabilization and modification processes through PTMs and MAPs. This is followed by an examination of PTMs' role in microtubule stability and their implications in neurodegenerative diseases.

The survey further explores MAPs' role in axon guidance and cytoskeletal remodeling, highlighting their interactions with microtubules and their importance in maintaining neuronal structure and function. The intricate relationship between cytoskeletal remodeling and neurodegenerative diseases is examined, emphasizing how disturbances in microtubule dynamics can drive disease pathogenesis, particularly in conditions like Parkinson's disease. This discussion highlights specific genetic mutations linked to microtubule dysfunction, such as those affecting MAP tau, and underscores the potential for targeted therapeutic interventions through regulating microtubule dynamics and using microtubule-targeting agents [24, 6].

The synthesis of key discussions highlights the critical role of microtubule dynamics, PTMs, and MAPs in neuronal morphogenesis and the pathogenesis of neurodegenerative diseases such as Parkinson's disease. The review underscores the interplay between these factors and their contribution to cellular functions, including intracellular transport and synaptic plasticity. Furthermore, it outlines promising future research avenues and potential therapeutic strategies aimed at targeting microtubule regulation and dysfunction, which may lead to innovative treatments for neurodegenerative conditions [24, 8, 26, 25, 27]. This structured approach facilitates a comprehensive understanding of the complex biological processes involved, offering insights into innovative methodologies and therapeutic strategies.The following sections are organized as shown in Figure 1.

2 Background and Definitions

2.1 Microtubule Dynamics

Microtubule dynamics, characterized by phases of polymerization and depolymerization, are crucial for maintaining neuronal structural and functional integrity. This dynamic instability is essential for intracellular transport and cellular architecture [28]. The regulation of microtubule length, influenced by dynamic instability, is vital for neuronal development and organization within cells. In neurons, microtubule dynamics facilitate axonal transport, crucial for moving organelles and proteins necessary for synaptic function and plasticity [17]. Motor proteins such as kinesin and dynein navigate these microtubule tracks, delivering essential cargoes vital for neuronal health and communication [29]. This transport system is integral to maintaining synaptic connectivity and supports cognitive functions like learning and memory [6]. Additionally, microtubule mechanical properties, modulated by geometric constraints and external forces, significantly influence cellular behaviors and neuronal structural integrity [30].

Post-translational modifications, including ubiquitin-like modifications, are crucial for maintaining microtubule dynamics, affecting the transport properties and distribution of motor proteins like Kinesin-3 [29]. These modifications allow adaptation to environmental changes and cellular demands. The interplay between microtubule dynamics and signaling pathways, such as TGF-, underscores their role in regulating neuronal morphogenesis and function [31]. Understanding microtubule dynamics is essential for elucidating mechanisms underlying neuronal development and addressing pathophysiological changes in neurodegenerative diseases [32]. Insights into these dynamics can guide therapeutic strategies aimed at stabilizing microtubules to mitigate neuronal dysfunction and disease progression [22]. Furthermore, BDNF signaling via TrkB.T1 in astrocyte morphological maturation highlights the broader significance of cytoskeletal dynamics in central nervous system development and function [33].

2.2 Neuronal Morphogenesis

Neuronal morphogenesis involves complex processes shaping neuron development, including cell migration, axon and dendrite formation, and synaptic connectivity, all vital for proper nervous system development [34]. This intricate process is influenced by genetic, molecular, and environmental factors guiding the structural and functional maturation of neurons [3]. The formation of the neural tube, a precursor to the central nervous system, exemplifies the challenges in neuronal morphogenesis, requiring precise coordination of cell-fate patterns and tissue shape reproducibility [35].

Microtubule dynamic instability is pivotal in neuronal morphogenesis, governing the assembly and disassembly of cytoskeletal structures necessary for cellular organization and intracellular transport [28]. This dynamic nature is crucial for axonal growth and guidance, essential for establishing functional neuronal networks [36]. Additionally, cell migration within the developing cerebral cortex is critical for proper cortical layering and connectivity [37]. Tissue morphology significantly influences the emergence of neural structures, highlighting the importance of the physical environment in directing neuronal development [38]. Cytokines, particularly from the TGF- family, are crucial in neuronal morphogenesis, modulating signaling pathways that affect neuronal shape and connectivity [31]. Proteins such as Cdk5 play dual roles in physiological and pathological contexts, underscoring the complexity of regulatory mechanisms involved in neuronal development [39].

Understanding factors contributing to neuronal morphogenesis is essential for elucidating developmental disorders and developing therapeutic strategies to address structural and functional deficits

in conditions such as autism spectrum disorders (ASD) [3]. Insights into these processes enhance comprehension of neural development and inform approaches to mitigate the impacts of genetic mutations and environmental factors on neuronal health and function [34].

2.3 Post-Translational Modifications (PTMs)

Post-translational modifications (PTMs) are vital biochemical processes occurring after protein synthesis, altering protein properties and functions, and playing significant roles in microtubule dynamics and neuronal function. PTMs such as phosphorylation, acetylation, methylation, and glutamylation regulate structural dynamics and interactions of microtubules with associated proteins, influencing processes essential for neuronal development [40]. Phosphorylation, a well-studied PTM, modulates protein interactions and signaling pathways, affecting microtubule-associated proteins (MAPs) like Tau, leading to altered microtubule stability and implications in neurodegenerative diseases.

Acetylation of tubulin enhances microtubule stability and affects interactions with motor proteins, influencing intracellular transport mechanisms crucial for neuronal health. Glutamylation, specific to tubulin, modulates microtubule stability and dynamics, impacting axonal transport and cell division. Methylation influences the structural dynamics of proteins interacting with microtubules, altering protein conformation and binding interactions, crucial for intracellular organization and chromosome segregation. This modulation can contribute to neurodegenerative disorders like Alzheimer's disease, where destabilized microtubules due to altered protein interactions are key factors [41, 42, 11, 43, 1].

Challenges in studying PTMs include generating antibodies that specifically recognize them, essential for understanding their roles in various biological processes [40]. Advanced visualization techniques are necessary to study PTMs and their effects on microtubules, as current methods face issues like photodamage and perturbation of microtubule properties. Understanding the intricate roles of PTMs in modulating microtubule dynamics is crucial for elucidating molecular mechanisms underlying neuronal development and the pathophysiology of neurodegenerative diseases, offering potential therapeutic targets for intervention.

2.4 Microtubule-Associated Proteins (MAPs)

Microtubule-associated proteins (MAPs) are essential for regulating and stabilizing microtubule dynamics, playing critical roles in neuronal morphogenesis and functionality. By binding to microtubules, these proteins influence stability, assembly, and interactions with other cytoskeletal components, facilitating intracellular transport and synaptic connectivity. MAPs are categorized into several functional groups, including motile MAPs, enzymes, microtubule nucleators, end-binding proteins, and structural MAPs, each contributing uniquely to the microtubule network's integrity and function [10].

Tau, a well-studied MAP, exemplifies the dual role of MAPs as stabilizers and inducers of microtubule formation. It regulates microtubule dynamics by promoting assembly and maintaining stability, crucial for axonal transport and neuronal architecture [42]. The competitive dynamics between MAP7 and tau illustrate the complex interplay within the cellular environment, affecting the distribution and balance of motor transport [26]. Furthermore, MAP2, MAP4, and tau uniquely alter microtubule properties, leading to distinct neurite morphologies, underscoring the specificity of MAP-mediated regulation of microtubule dynamics [25].

Recent studies have identified novel MAPs such as WAVE DAMPENED2-LIKE (WDL), emphasizing the necessity for balanced regulation of microtubule dynamics to maintain stable tip growth and overall cellular integrity [44]. The intricate interactions between MAPs and microtubules are complicated by the allosteric properties of tubulin, suggesting a need for further exploration into how MAPs influence these dynamics [1].

Advancements in proteomic technologies enhance our understanding of MAPs, revealing significant roles in health and disease contexts. Investigating MAPs presents potential for advancing therapeutic strategies for neurodegenerative diseases characterized by dysregulated microtubule dynamics, such as Parkinson's disease. This condition is increasingly recognized for its association with early cytoskeletal dysfunction, where alterations in MAP expression and function contribute to impaired neuronal transport and overall cellular health. Targeting the regulatory mechanisms of MAPs and

their interactions with microtubules may lead to innovative treatments addressing underlying cellular abnormalities common in these disorders [24, 26, 45]. Understanding the molecular mechanisms by which MAPs stabilize and guide microtubules is crucial for elucidating their contributions to neuronal development and function, offering potential avenues for intervention in neurodegenerative conditions.

2.5 Axon Guidance

Axon guidance is a fundamental process in neuronal development, ensuring precise navigation of axons to their target destinations, crucial for establishing functional neural circuits and proper neuronal connectivity [46]. This intricate process is orchestrated by various axon guidance molecules (AGMs), including Netrins, Semaphorins, Ephrins, and Slits, which interact with specific receptors on the growth cone surface, initiating intracellular signaling pathways that direct axonal growth and steering. For example, Netrin-1 mediates axonal guidance through interactions with receptors such as DCC, Neogenin, and Unc5A-D, highlighting its critical role in axon pathfinding [21].

Axon guidance involves a series of decision points where growth cones, the motile structures at the tips of growing axons, respond to environmental cues. Directional chemical cues are particularly important as they affect microtubule polarization within neuronal growth cones, essential for accurate neuronal pathfinding [47]. The midline crossing of axons is a pivotal event in the development of commissural axons, regulated by guidance cues that ensure axons reach and cross the midline to form bilateral neural circuits [48]. The floor plate serves as an intermediate target, providing essential signals that guide axons across the midline, underscoring the importance of spatial and temporal regulation of guidance cues in this process [49].

AGMs also play a role in regulating neuroinflammation, although their implications in neurodegenerative diseases are not yet fully understood [20]. Disorders such as Duane Retraction Syndrome (DRS), Horizontal Gaze Palsy with Progressive Scoliosis (HGPPS), and Congenital Fibrosis of the Extraocular Muscles type 3 (CFEOM3) present significant challenges due to their genetic and developmental implications, further emphasizing the significance of axon guidance in both central and peripheral nervous system development [46].

The complexity of receptor interactions and the diversity of signaling outputs present significant challenges in studying these processes in vivo, necessitating further research to elucidate the underlying mechanisms [12]. Computational models have been developed to better understand the mechanisms of axon guidance, shedding light on how axons overcome environmental challenges and decision points during growth [50]. However, quantitatively studying axon guidance and growth dynamics from individual primary mammalian neurons in response to biochemical gradients remains a challenge [5].

2.6 Cytoskeletal Remodeling

Cytoskeletal remodeling refers to the dynamic reorganization of the cytoskeleton, a complex network of protein filaments, including microtubules, actin filaments, and intermediate filaments, which collectively provide structural support and facilitate various cellular functions such as intracellular transport, cell division, and morphogenesis [51]. This dynamic behavior is particularly crucial for neuronal structure and function, influencing processes such as axon guidance, synaptic plasticity, and cellular migration. The cytoskeleton's adaptability to environmental changes is pivotal for maintaining cellular integrity and enabling processes like neuronal migration and differentiation, essential for proper neuronal morphology and connectivity [2].

Interactions between motor proteins and the cytoskeletal network are complex and inadequately modeled in previous studies, highlighting the need for a deeper understanding of these dynamics [4]. The mechanical properties of cells, including their ability to adapt to dynamic loading, are closely linked to cytoskeletal remodeling. This adaptability is essential for processes like neuronal migration and differentiation, which require precise modulation of cytoskeletal components to achieve proper neuronal morphology and connectivity [30]. The rigidity and steric hindrances imparted by the cytoskeletal network can lead to anomalous subdiffusion, while motor-driven restructuring processes can induce athermal superdiffusion, illustrating the complex interplay between passive and active forces in cytoskeletal dynamics [52].

In neuronal development, cytoskeletal remodeling is influenced by nuclear migration dynamics, where microtubules play a pivotal role in shaping cellular behavior and morphology. Kinesin-8 proteins are implicated in various aspects of microtubule dynamics, including catastrophe and rescue frequencies, critical for maintaining the dynamic instability necessary for effective cytoskeletal remodeling [53]. RUFY proteins serve as adaptors linking membrane trafficking and cytoskeletal dynamics, further emphasizing the interconnected nature of these cellular processes [17].

The role of glial cells, particularly microglia and oligodendrocyte precursor cells, is essential in cortical morphogenesis, as they significantly contribute to cytoskeletal remodeling through cell-type-specific mechanisms facilitating precise cell migration, intercellular signaling, and the establishment of neural circuits necessary for proper brain function. This underscores the critical interplay between various glial populations and their influence on the spatial and temporal organization of neural cells during embryonic development, ultimately affecting the structural and functional integrity of the cerebral cortex [33, 54, 37]. These cells interact with the neuronal cytoskeleton to facilitate the development and maintenance of the central nervous system, highlighting the multifaceted nature of cytoskeletal remodeling in neuronal structure and function. Understanding these processes is vital for elucidating the mechanisms underlying neuronal development and developing therapeutic interventions for neurodegenerative disorders.

The intricate processes underlying neuronal development are significantly influenced by the dynamics of microtubules. These structures not only provide a scaffold for cellular architecture but also play critical roles in various neuronal functions, including stabilization and modification. As illustrated in Figure 2, the hierarchical structure of microtubule dynamics is essential for understanding neuronal morphogenesis. This figure encapsulates key concepts such as the regulatory mechanisms by microtubule-associated proteins (MAPs) and post-translational modifications (PTMs), as well as the implications of these dynamics in neurodegenerative diseases. Furthermore, it highlights computational models that simulate axon guidance, thereby offering a comprehensive overview of how microtubules contribute to synaptic plasticity and overall neuronal function.

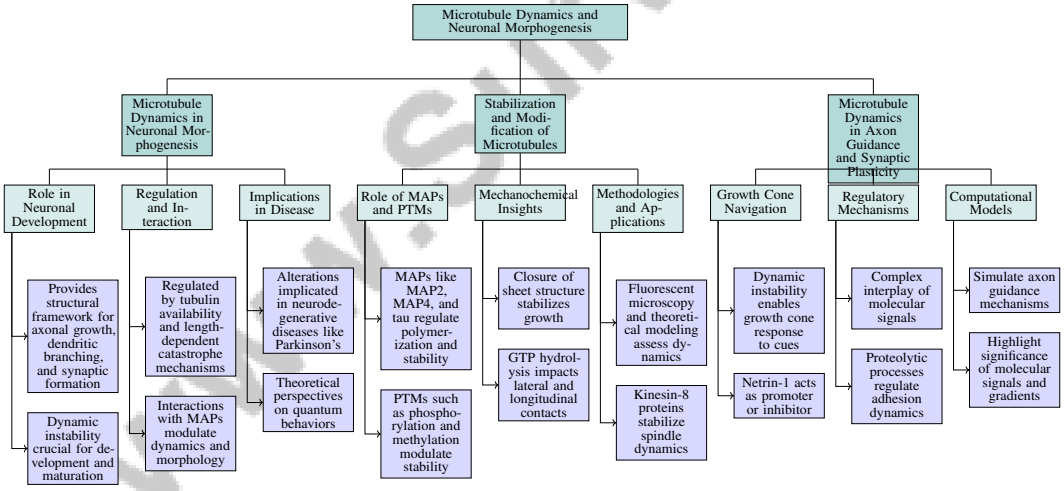

Figure 2: This figure illustrates the hierarchical structure of microtubule dynamics in neuronal morphogenesis, stabilization, and modification, as well as their roles in axon guidance and synaptic plasticity. Key concepts include the structural framework for neuronal development, regulation by MAPs and PTMs, implications in neurodegenerative diseases, and computational models simulating axon guidance.

3 Microtubule Dynamics and Neuronal Morphogenesis

3.1 Microtubule Dynamics in Neuronal Morphogenesis

Microtubule dynamics are integral to neuronal morphogenesis, providing a structural framework for axonal growth, dendritic branching, and synaptic formation. Their dynamic instability, marked by cycles of polymerization and depolymerization, is crucial for neuronal development and maturation,

influenced by mechanical stability and chemical energy fluctuations [55]. Regulation of microtubule length, governed by tubulin availability and length-dependent catastrophe mechanisms, sustains the dynamic instability essential for neuronal development [56].

Interactions between microtubules and microtubule-associated proteins (MAPs) significantly modulate these dynamics, impacting neuronal morphology and neural circuit formation [10]. Tau, a prominent MAP, stabilizes microtubules and actively participates in their assembly, underscoring its role in maintaining neuronal architecture [42]. The spatial organization of cytoskeletal networks, including microtubule arrangement, influences cargo transport efficiency within neurons, affecting axonal transport and synaptic connectivity [4]. Additionally, Cdk5 substrates interact with the cytoskeleton, influencing microtubule dynamics crucial for neuronal morphogenesis [6].

To further elucidate these concepts, Figure 3 illustrates the hierarchical classification of key concepts related to microtubule dynamics in neuronal morphogenesis. This figure highlights the intricate relationships between microtubule dynamics, their impacts on neuronal structure, and implications for neurodegenerative diseases, thereby providing a visual representation that complements the textual analysis.

Alterations in microtubule dynamics are implicated in neurodegenerative diseases, such as Parkinson's disease, where disruptions in cytoskeletal integrity contribute to disease progression [24]. Theoretical perspectives suggest that microtubules in neurons may exhibit quantum behaviors disrupted by amyloid nanotubes, leading to cognitive impairment and enhancing our understanding of neuronal morphogenesis [32]. Furthermore, TGF- signaling through the Smad-dependent pathway inhibits neuronal morphogenesis by repressing CRMP2 expression, illustrating the regulatory mechanisms influencing microtubule dynamics and neuronal development [31]. Understanding these dynamics offers potential therapeutic targets for neurodegenerative diseases, providing a framework for future research and intervention strategies.

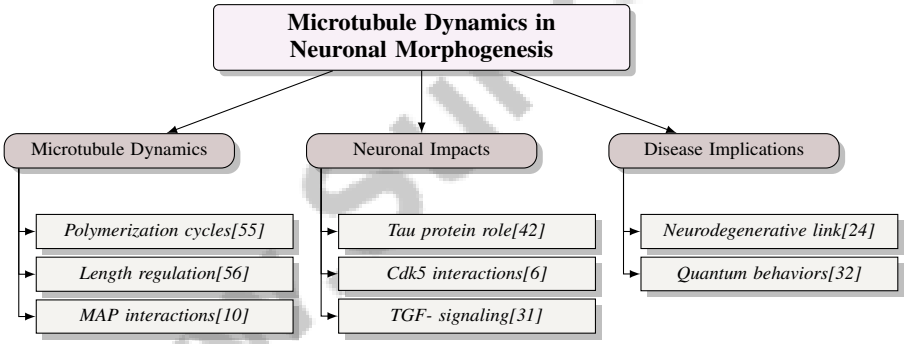

Figure 3: This figure illustrates the hierarchical classification of key concepts related to microtubule dynamics in neuronal morphogenesis, highlighting microtubule dynamics, their impacts on neuronal structure, and implications for neurodegenerative diseases.

3.2 Stabilization and Modification of Microtubules

Microtubule stabilization and modification are crucial for maintaining the structural integrity and functional adaptability of neuronal cells. Microtubule dynamics, essential for neuronal morphogenesis and synaptic connectivity, are finely regulated by various MAPs, including MAP2, MAP4, and tau, alongside post-translational modifications (PTMs). These MAPs promote microtubule polymerization and stability while influencing their physical properties, such as flexibility and morphology, which affect neurite branching and dendritic spine integrity. Tau enhances microtubule rigidity, while MAP6 stabilizes actin filaments within dendritic spines, highlighting the interconnectedness of microtubule dynamics and synaptic plasticity. The competition among MAPs for binding sites on microtubules is critical for regulating motor transport, ensuring proper intracellular cargo distribution essential for neuronal function [24, 57, 26, 25, 27].

MAPs play a pivotal role in microtubule stabilization by modulating interactions with other cellular components. For example, MAP7 displaces tau from the microtubule lattice, enhancing kinesin-based transport while inhibiting kinesin-3, illustrating the competitive dynamics influencing microtubule interactions and transport efficacy [26]. PTMs, such as phosphorylation and methylation, are vital for

modulating microtubule stability and interactions, with the 'tubulin code' categorizing modifications that influence microtubule behavior [58]. These modifications can alter MAP binding affinity, affecting stability and function. The 'arginine claw' structural motif facilitates transient interactions with intermediate filaments under specific phosphorylation and methylation conditions, crucial for maintaining cytoskeletal integrity [59].

Mechanochemical modeling of microtubule dynamics indicates that the closure of the sheet structure stabilizes growth, requiring a minimum length of two dimers for effective stabilization [55]. GTP hydrolysis leads to a two-step weakening of lateral contacts while reinforcing longitudinal contacts, triggering microtubule catastrophe due to the inability of lateral contacts to counteract stored strain energy [60]. The interactions of microtubules with the cell cortex significantly contribute to their stabilization and modification, influencing spindle dynamics during cell division [61]. Kinesin-8 proteins, such as Klp5 and Klp6, are critical for stabilizing spindle dynamics and ensuring accurate chromosome movements during mitosis [53].

Advanced methodologies, including fluorescent microscopy and theoretical modeling, have been employed to assess motor dynamics and cargo binding kinetics, enhancing our understanding of the processes regulating microtubule stability and function in neuronal contexts [29].

3.3 Microtubule Dynamics in Axon Guidance and Synaptic Plasticity

Microtubule dynamics are pivotal in axon guidance and synaptic plasticity, providing the structural framework necessary for growth cone navigation through complex neural environments. The dynamic instability of microtubules enables precise regulation of growth cone behavior, allowing responses to extracellular cues and navigation towards synaptic targets [5]. This dynamic behavior is essential for establishing and maintaining neuronal connectivity, underpinning the growth cone's ability to interpret guidance signals such as Netrin-1, which can act as both a promoter and inhibitor of axon growth depending on the context [21].

Regulation of axon guidance involves a complex interplay of molecular signals, including axon guidance receptors modulated at transcriptional, translational, and post-translational levels [12]. This multi-level regulation is critical for the growth cone's ability to integrate diverse signals and execute navigational decisions. Additionally, microfluidic gradient generator arrays have demonstrated that hippocampal axons exhibit a biphasic response to Netrin-1 gradients, contingent on concentration and angle of incidence [5].

Proteolytic processes, such as calpain-mediated proteolysis, are crucial for regulating adhesion dynamics within growth cones, influencing microtubule interactions and axon guidance [62]. Furthermore, the calcium-sensing protein STIM1 is hypothesized to couple microtubule dynamics with endoplasmic reticulum (ER) remodeling, regulating calcium signaling in growth cones and influencing axon pathfinding [63].

Computational models simulating axon guidance offer insights into the activity-independent mechanisms governing this process [50]. These models emphasize the significance of microtubule dynamics in growth cone behavior and axon pathfinding, highlighting the importance of molecular signals and their concentration gradients [64]. Additionally, the identification of key genes and proteins associated with disorders such as Duane Retraction Syndrome (DRS), Horizontal Gaze Palsy with Progressive Scoliosis (HGPPS), and Congenital Fibrosis of the Extraocular Muscles type 3 (CFEOM3) facilitates comparisons of molecular mechanisms involved in these disorders, underscoring the critical role of axon guidance in central and peripheral nervous system development [46].

4 Role of Post-Translational Modifications (PTMs)

4.1 PTMs in Neuronal Development

Post-translational modifications (PTMs) are critical in modulating microtubule dynamics, influencing neuronal development by affecting microtubule stability and interactions with associated proteins. Phosphorylation, acetylation, and ubiquitination are key PTMs that alter protein conformation and function, guiding neuronal differentiation and synaptic connectivity [40]. Phosphorylation, in particular, induces structural changes in proteins, modulating their binding affinity to microtubules and regulating neuronal morphogenesis [11]. The dynamic instability of microtubules, characterized

by growth and shrinkage phases, is controlled by PTMs that modulate microtubule-associated proteins (MAPs) interactions [1, 10]. The regulation of phosphate release via PTMs is crucial for microtubule dynamics, underscoring their role in neuronal structure development [56].

As illustrated in Figure 4, the hierarchical structure of PTMs in neuronal development highlights not only the key modifications involved but also their significant roles in microtubule dynamics and broader implications within the central nervous system (CNS). Kinesin-8 motor proteins, regulated by PTMs, are pivotal in modulating microtubule dynamics during neuronal mitosis. These modifications influence chromosome segregation and spindle stability; the absence of kinesin-8 leads to microtubule destabilization and disorganized chromosome movements. Kinesin-8 proteins, such as Klp5 and Klp6 in fission yeast, are essential for maintaining spindle length stability and accurate chromosome alignment, with their deletion causing aberrant kinetochore movements and fluctuating spindle lengths [65, 66, 53, 26]. These findings highlight the critical role of PTMs in maintaining microtubule stability during neuronal development.

The regulation of Cdk5 activity through PTMs illustrates their influence on microtubule stability, as Cdk5 is vital for cytoskeletal integrity during neuronal development [6]. Advanced antibody generation techniques targeting PTMs enhance our understanding of these modifications in neuronal development [40]. Mechanical stimuli, alongside PTMs, significantly influence cytoskeletal responses and stem cell differentiation pathways, impacting neuronal development [2]. This interplay illustrates the complexity of regulatory mechanisms governing neuronal development.

Moreover, Brain-Derived Neurotrophic Factor (BDNF) affects astrocyte morphology through the TrkB.T1 receptor, showcasing PTMs' broader role in central nervous system development, as astrocytes contribute to the neuronal microenvironment [33]. The use of microfluidic gradient generator arrays for large-scale axon guidance studies further emphasizes PTMs' significance in neuronal development, providing insights into dynamic neuron-environment interactions [5].

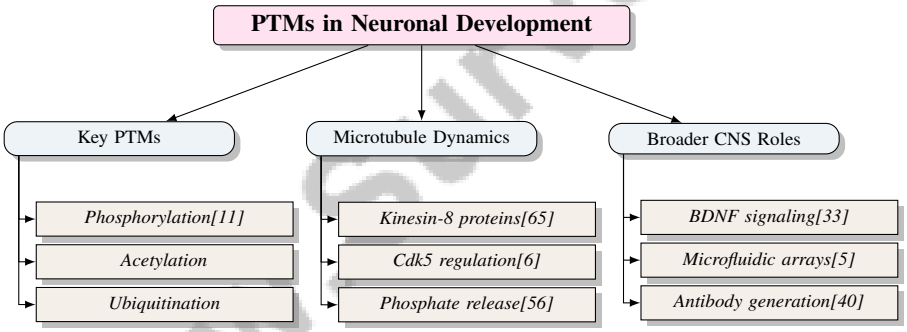

Figure 4: This figure illustrates the hierarchical structure of post-translational modifications (PTMs) in neuronal development, highlighting key PTMs, their role in microtubule dynamics, and broader roles in the central nervous system (CNS).

4.2 PTMs and Neurodegenerative Diseases

Post-translational modifications (PTMs) significantly influence the pathogenesis of neurodegenerative diseases by affecting protein stability, aggregation, and interactions within neuronal environments. Phosphorylation and ubiquitination of proteins like tau are crucial in modulating aggregation properties, central to Alzheimer's disease progression [67]. The complexity of PTM interactions and identifying specific modifications regulating protein stability necessitate a comprehensive understanding of underlying molecular mechanisms [41].

The heterodimer model effectively captures tau protein misfolding dynamics, especially under varying concentrations of healthy proteins, emphasizing PTMs' role in disease progression [16]. Amyloid nanotubes' interference with quantum processes in microtubules significantly contributes to consciousness impairment in Alzheimer's disease, suggesting potential therapeutic interventions [32].

PTMs are integral to modulating the unfolded protein response (UPR), with oscillatory UPR behavior presenting a therapeutic target for prion diseases. Adjusting specific parameters can significantly alter UPR intensity, indicating that targeting PTMs could enhance protein homeostasis and mitigate neurodegenerative processes [22]. The dynamics of protein aggregation, as shown by the Network

Transport Model (NTM), underscore PTMs' critical role in disease progression, revealing how microscopic parameters, including tau aggregation and transport, contribute to macroscopic pathology [67].

Additionally, PTMs influence the mechanical properties and stability of proteins like SOD1, although evaluating these effects remains challenging due to a lack of robust methods and uniform benchmarks [41]. This highlights the need for advanced techniques to elucidate the relationship between mutations, PTMs, and disease progression. Exploring PTMs in the context of tumor microenvironment (TME) interactions offers insights into their broader implications in cellular heterogeneity and disease progression, which can be extrapolated to neurodegenerative diseases [68].

5 Microtubule-Associated Proteins (MAPs) and Axon Guidance

5.1 MAPs and Microtubule Dynamics in Axon Guidance

Method Name	Functional Role	Regulatory Mechanisms	Research Approaches
MPM[47]	Dynamic Instability	Reaction-diffusion Network	Computational Model
NCFAG[54]	Axon Guidance Impact	Distinct Signaling Pathways	Time-lapse Imaging
KDA[53]	Microtubule Dynamics Impact	Interactions With Cues	Computational Models
MGGA[5]	Axon Guidance	Transcription Factors	Experimental Studies

Table 1: Summary of methods exploring the roles of microtubule-associated proteins (MAPs) in axon guidance, detailing their functional roles, regulatory mechanisms, and research approaches. The table highlights diverse methodologies employed to elucidate the impact of MAPs on microtubule dynamics and axon guidance, integrating computational models and experimental studies.

Microtubule-associated proteins (MAPs) are essential in modulating microtubule dynamics, crucial for axon guidance and growth cone navigation in the neural environment [55]. MAP7, for example, enhances kinesin-1 transport by competing with tau, underscoring MAPs' role in growth cone responses to guidance cues like netrins and semaphorins. Despite limited characterization of many MAPs, computational models reveal their significance in regulatory networks that guide growth cone behavior, influenced by guidance cue concentration and neuronal activity [10, 50]. Integrating mechanical and chemical dynamics provides insights into microtubule polarization within growth cones, vital for neuronal pathfinding [47]. Table 1 provides a comprehensive overview of various methods utilized to investigate the influence of microtubule-associated proteins on axon guidance, emphasizing their functional roles, regulatory mechanisms, and the research approaches adopted.

Glial cells contribute to axon guidance by modulating guidance cues during brain assembly [54]. Transcription factors interacting with axon guidance cues also influence microtubule dynamics, evident in retinal neuron development [69]. Kinesin-8 deletion studies highlight MAPs' role in maintaining microtubule dynamics essential for axonal guidance [53]. The frameworks by [46] and [5] provide pathways for understanding axon guidance disorders and axon growth dynamics, respectively.

5.2 Role of MAPs in Growth Cone Behavior

MAPs regulate growth cone behavior by modulating cytoskeletal dynamics, crucial for axon pathfinding. The growth cone relies on the interplay of actin filaments and microtubules for navigation. MAPs like tau and MAP1B stabilize microtubules, enhancing structural integrity and enabling growth cone responses to guidance cues [70]. This stabilization is essential for interpreting cues like netrins and semaphorins, directing axonal growth [70].

MAPs also facilitate the localization and transport of signaling molecules within the growth cone, affecting signaling pathways that govern motility and guidance. They modulate interactions between microtubules and actin filaments, coordinating cytoskeletal remodeling in response to cues. This involves calcium signaling regulation through the ER and its calcium sensor, STIM1, crucial for steering growth cones towards attractive cues like BDNF and away from repulsive ones like semaphorin3a [12, 63].

5.3 MAPs and Axon Guidance Cues

MAPs are pivotal in facilitating interactions between microtubules and axon guidance cues, ensuring precise axonal navigation. This interaction is essential for directing growth cone pathfinding via guidance molecules such as netrins, semaphorins, ephrins, and slits [70]. These cues activate intracellular signaling cascades that MAPs modulate to stabilize and reorganize microtubules [21]. MAPs like tau and MAP1B affect microtubule stability and dynamics, influencing growth cone responsiveness [10]. PTMs further modulate MAP interactions, altering their regulatory functions [11, 40].

The spatial and temporal regulation of MAP interactions is crucial for forming functional neuronal circuits. Computational models highlight MAP-mediated regulation's role in axon guidance, emphasizing their contribution to integrating signaling pathways that guide axonal growth [50].

5.4 MAPs in Cytoskeletal Remodeling

MAPs are vital for cytoskeletal remodeling, essential for neuronal function and integrity. They stabilize and organize cytoskeletal components, facilitating processes like intracellular transport and morphogenesis. MAPs such as tau, MAP2, and MAP4 modulate microtubule stability and dynamics, influencing neuronal architecture [25]. Cytoskeletal remodeling requires coordinated MAP action, crucial for axonal transport and synaptic plasticity, essential for cognitive functions [6]. MAPs regulate microtubule dynamics, affecting polymerization rates and cytoskeletal network stability [1].

MAPs are also involved in the cross-talk between microtubules and actin filaments, vital for growth cone motility and axon guidance [70]. This interaction influences cytoskeletal mechanical properties, impacting cellular behaviors like migration [2]. During neuronal development, MAPs contribute to cytoskeletal remodeling necessary for synaptic connection formation and maintenance [4]. Their role in microtubule dynamics during axonal growth is crucial for establishing functional neuronal circuits [5].

5.5 Therapeutic Implications of MAPs

MAPs offer significant therapeutic potential for neurodegenerative diseases due to their role in modulating microtubule dynamics. Insights into axon guidance mechanisms highlight MAPs as therapeutic targets for neurological disorders [48]. Targeting tau is emphasized for Alzheimer's disease and tauopathies, given its role in microtubule stabilization and pathological aggregation [42]. The calcium-dependent regulation of growth cone motility by calpain suggests MAPs as targets for interventions in diseases with impaired axonal growth [62]. Targeting metabolic dysfunction in NPCs presents strategies for conditions like Leigh syndrome [34].

In neurodegenerative diseases, targeting casein kinase 1 (CK1) with inhibitors represents a promising therapeutic approach, similar to cancer treatment [71]. This underscores MAP-targeted therapies' applicability across pathological contexts. Exploring MAPs in cancer metastasis as therapeutic targets highlights the need for research into MAP mechanisms and drug development trends [45]. The novel role of MAP6 in actin dynamics suggests therapeutic targets for disorders linked to MAP6 dysfunction [27]. Cdk5, a kinase interacting with MAPs, is a promising drug development target for neurological disorders due to its role in regulating microtubule dynamics [6].

Targeting MAPs extends beyond neurodegenerative diseases, offering innovative approaches to cancer and neuropsychiatric disorders. Ongoing investigations into MAPs across diverse conditions, particularly cancer metastasis and neurodegenerative diseases, will deepen understanding of their roles as therapeutic targets, elucidating molecular mechanisms and guiding treatment strategy development [72, 45, 73, 27, 74].

6 Cytoskeletal Remodeling and Neurodegenerative Diseases

The relationship between cytoskeletal dynamics and neuronal health is crucial in neurodegenerative diseases, where the cytoskeleton supports vital cellular processes such as intracellular transport and signaling. Understanding cytoskeletal remodeling mechanisms is essential for elucidating the pathophysiology of these disorders. This section examines disruptions in microtubule dynamics,

highlighting their role in neurodegenerative disease progression and the broader implications of cytoskeletal alterations on neuronal function.

6.1 Disruptions in Microtubule Dynamics

Disruptions in microtubule dynamics are central to neurodegenerative disease pathogenesis, compromising neuronal integrity and function. The dynamic instability of microtubules, involving polymerization and depolymerization phases, maintains neuronal architecture and facilitates intracellular transport. Imbalances in this dynamic can impair axonal transport and synaptic function, hallmarks of Alzheimer's and Parkinson's diseases [32]. Amyloid nanotubes disrupt microtubule function, affecting cognitive processes and contributing to neurodegeneration by compromising neuronal structural integrity [32]. Theoretical models highlight gaps in understanding microtubule growth, particularly during the sheet-to-tube transition.

The interplay between microtubule-associated proteins (MAPs) and microtubules is crucial for regulating motor transport within neurons. MAPs like MAP7 and tau influence motor proteins such as kinesin and dynein, with competition among these proteins affecting transport distribution and balance essential for neuronal health. Disruptions in this balance can lead to neurodegenerative diseases, emphasizing the importance of understanding these interactions for therapeutic interventions [24, 45, 42, 26, 27]. Dysregulation of kinases like Cdk5, interacting with microtubules, further contributes to neurodegenerative pathogenesis.

Post-translational modifications (PTMs) significantly modulate microtubule dynamics, yet their regulatory mechanisms and implications remain limited. The complexity of PTM interactions complicates understanding their role in neurodegenerative diseases. Current models often oversimplify molecular mechanisms and patient heterogeneity or are computationally intensive, limiting practical applications. Advanced methodologies, such as machine learning and multivariate nonlinear mixed effects models, are needed to integrate high-dimensional data and account for individual variability in disease trajectories, facilitating more accurate predictions and interventions [67, 75, 68, 73, 74].

Netrin-1, continuously expressed in the adult nervous system, plays a dual role in neuronal function. While guiding axonal growth during development, its persistent presence inhibits axon regeneration following injury, exacerbating neurodegenerative disease challenges by hindering axonal repair mechanisms. Understanding Netrin-1's regulatory mechanisms and its receptors may reveal new therapeutic targets for enhancing axonal regeneration and mitigating neurodegeneration effects [12, 70, 76, 21, 20]. The complexity of axon guidance molecules' interactions and their dual roles in promoting and resolving inflammation pose significant challenges for understanding their mechanisms.

Integrating advanced imaging techniques and computational models that gather rich statistical data while minimizing shear stress and maintaining cell viability will be crucial for improving our understanding of microtubule dynamics in neurodegenerative diseases [5].

6.2 Cytoskeletal Remodeling and Protein Aggregation

Cytoskeletal remodeling is intricately linked to protein aggregation in neurodegenerative conditions, where disruptions in cytoskeletal dynamics contribute to pathological protein accumulation. The cytoskeleton, comprising microtubules, actin filaments, and intermediate filaments, continuously remodels to maintain cellular integrity and facilitate intracellular transport and signaling [4]. Aberrant cytoskeletal dynamics in neurodegenerative diseases lead to impaired axonal transport, resulting in the accumulation of misfolded proteins and the formation of aggregates such as amyloid-beta plaques and neurofibrillary tangles [16].

The relationship between cytoskeletal components and protein aggregation is further complicated by MAPs, which regulate microtubule stability and dynamics. Dysregulation of MAPs, particularly tau, is a hallmark of Alzheimer's disease, where hyperphosphorylated tau detaches from microtubules, destabilizing them and leading to aggregation into neurofibrillary tangles [10]. This process disrupts the cytoskeletal network and impairs axonal transport, exacerbating the accumulation of pathological proteins and contributing to neuronal dysfunction and cell death [42].

PTMs are crucial in cytoskeletal remodeling and protein aggregation in neurodegenerative conditions. Modifications such as phosphorylation, acetylation, and ubiquitination influence protein interactions

and stability, affecting aggregation propensity [40]. Specifically, tau phosphorylation alters its binding affinity to microtubules, promoting detachment and aggregation [11]. The dynamic instability of microtubules, characterized by rapid growth and shrinkage phases, is essential for neuronal function; disruptions in these dynamics can lead to pathological protein aggregation and neurodegeneration [1].

Computational models and experimental techniques elucidating the interactions between cytoskeletal components and aggregated proteins advance the mechanistic understanding of cytoskeletal remodeling and protein aggregation. These models provide insights into the molecular mechanisms underlying neurodegenerative diseases, emphasizing the need to target cytoskeletal dynamics and protein aggregation pathways for therapeutic intervention [67].

6.3 Therapeutic Targets and Future Directions

Exploring therapeutic targets for neurodegenerative diseases requires a multifaceted approach, considering the intricate interplay of molecular and cellular mechanisms. MAPs and PTMs have emerged as promising targets, particularly in diseases characterized by protein aggregation, such as tauopathies. The significant role of MAPs in preserving microtubule integrity and dynamics highlights their therapeutic implications not only in neurodegenerative diseases, like Parkinson's disease, but also in male infertility, where microtubule dynamics regulation is crucial for spermatogenesis. Disturbances in microtubule dynamics adversely affect cellular processes in both contexts, suggesting that targeting MAPs could offer novel treatment strategies [24, 45, 57].

Future research should prioritize expanding antibody libraries for PTMs to identify novel therapeutic targets in neurodegenerative diseases [40]. Additionally, integrating mechanical, biochemical, and physical cues into advanced materials and therapies can effectively guide stem cell differentiation and tissue regeneration, offering new intervention avenues [2]. Modulating signaling pathways, particularly those involving Brain-Derived Neurotrophic Factor (BDNF), presents another potential therapeutic target, especially in neurodevelopmental disorders where these pathways are disrupted [33].

Developing visualization recommendation systems, such as MitoVis, can streamline user experiences and enhance research functionality, providing valuable tools for analyzing complex biological data and informing therapeutic strategies [7]. Furthermore, investigating the therapeutic potential of targeting RUFY proteins, which are involved in cellular trafficking and cytoskeletal dynamics, warrants further exploration as a strategy for addressing neurodegenerative diseases [17].

To advance therapeutic development, future research should focus on elucidating MAP concentration regulatory mechanisms, their interactions with the tubulin code, and their roles in cellular signaling and transport [10]. Expanding datasets to include more PTMs and utilizing advanced computational models will enhance understanding of their structural implications and facilitate targeted therapy development [11]. By refining existing models and exploring new therapeutic targets, future research can contribute to effective interventions for these complex conditions.

7 Conclusion

The exploration of microtubule dynamics, post-translational modifications (PTMs), and microtubule-associated proteins (MAPs) reveals their pivotal roles in neuronal morphogenesis and the progression of neurodegenerative diseases. The inherent dynamic instability of microtubules, characterized by phases of polymerization and depolymerization, is crucial for sustaining neuronal architecture and ensuring efficient intracellular transport. Disruptions in these processes are linked to impaired axonal transport and synaptic dysfunction, contributing to conditions such as Alzheimer's and Parkinson's diseases. Understanding the biochemical and mechanical factors that influence microtubule dynamics is vital for unraveling cellular functions.

PTMs play a significant role in modulating microtubule stability and interactions with associated proteins, thereby influencing neuronal development and synaptic connectivity. These modifications lead to changes in protein conformation and function, guiding neuronal differentiation. Future studies should delve deeper into the effects of phosphorylation on MAPs and their interactions with microtubules to build on current knowledge. Additionally, understanding the dynamic behavior of cytoskeletal networks and their impact on transport efficiency, as well as the regulatory mechanisms that optimize transport, remains a critical area of research.

MAPs are integral to regulating microtubule dynamics during axon guidance, enhancing the growth cone's sensitivity to environmental signals. Their modulation of microtubule dynamics is essential for establishing neuronal connectivity and forming neural circuits. The interaction between MAPs and axon guidance molecules is crucial for directing growth cone navigation, emphasizing the importance of MAPs in neuronal connectivity.

Future research directions should focus on elucidating the molecular mechanisms underlying dynamic instability, exploring interactions between microtubules and other cytoskeletal elements, and incorporating complex biophysical and signaling features into models to enhance their biological relevance. Efforts should also be directed toward experimentally validating computational predictions and investigating ALS-associated mutations to understand their impact on SOD1 stability and function. The development of specific Cdk5 inhibitors that can differentiate between its beneficial and detrimental effects offers a promising therapeutic strategy.

References

[1] Gary J Brouhard and Luke M Rice. Microtubule dynamics: an interplay of biochemistry and mechanics. *Nature reviews Molecular cell biology*, 19(7):451–463, 2018.

[2] Vina DL Putra, Kristopher A Kilian, and Melissa L Knothe Tate. Biomechanical, biophysical and biochemical modulators of cytoskeletal remodelling and emergent stem cell lineage commitment. *Communications Biology*, 6(1):75, 2023.

[3] Annie Kathuria, Paulina Nowosiad, Ravi Jagasia, Stefan Aigner, RD Taylor, Laura Christiana Andreae, NJF Gatford, Walter Lucchesi, Deepak Prakash Srivastava, and Jack Price. Stem cell-derived neurons from autistic individuals with shank3 mutation show morphogenetic abnormalities during early development. *Molecular psychiatry*, 23(3):735–746, 2018.

[4] David Ando, Nickolay Korabel, Kerwyn Casey Huang, and Ajay Gopinathan. Cytoskeletal network morphology regulates intracellular transport dynamics, 2016.

[5] Nirveek Bhattacharjee and Albert Folch. Large-scale microfluidic gradient arrays reveal axon guidance behaviors in hippocampal neurons. *Microsystems & Nanoengineering*, 3(1):1–14, 2017.

[6] Kavita Shah and Debomoy K Lahiri. A tale of the good and bad: Remodeling of the microtubule network in the brain by cdk5. *Molecular neurobiology*, 54:2255–2268, 2017.

[7] JunYoung Choi, Hakjun Lee, Suyeon Kim, Seok-Kyu Kwon, and Won-Ki Jeong. Mitovis: A visually-guided interactive intelligent system for neuronal mitochondria analysis, 2021.

[8] Anna C Nelson, Melissa M Rolls, Maria-Veronica Ciocanel, and Scott A McKinley. Minimal mechanisms of microtubule length regulation in living cells, 2024.

[9] Microtubules and microtubule-ass.

[10] Satish Bodakuntla, AS Jijumon, Cristopher Villablanca, Christian Gonzalez-Billault, and Carsten Janke. Microtubule-associated proteins: structuring the cytoskeleton. *Trends in cell biology*, 29(10):804–819, 2019.

[11] Pierrick Craveur, Tarun Narwani, Joseph Rebehmed, and Alexandre de Brevern. Investigation of the impact of ptms on the protein backbone conformation, 2019.

[12] Yixin Zang, Karina Chaudhari, and Greg J Bashaw. New insights into the molecular mechanisms of axon guidance receptor regulation and signaling. *Current topics in developmental biology*, 142:147–196, 2021.

[13] Structural and mechanical remode.

[14] Aliza P Wingo, Eric B Dammer, Michael S Breen, Benjamin A Logsdon, Duc M Duong, Juan C Troncosco, Madhav Thambisetty, Thomas G Beach, Geidy E Serrano, Eric M Reiman, et al. Large-scale proteomic analysis of human brain identifies proteins associated with cognitive trajectory in advanced age. *Nature communications*, 10(1):1619, 2019.

[15] Brittany N Dugger and Dennis W Dickson. Pathology of neurodegenerative diseases. *Cold Spring Harbor perspectives in biology*, 9(7):a028035, 2017.

[16] Paola F. Antonietti and Mattia Corti. Numerical modelling of protein misfolding in neurodegenerative diseases: a computational study, 2024.

[17] Rémy Char and Philippe Pierre. The rufys, a family of effector proteins involved in intracellular trafficking and cytoskeleton dynamics. *Frontiers in cell and developmental biology*, 8:779, 2020.

[18] Abdulahad Bayraktar, Tugba Onal-Suzek, Baris Ethem Suzek, and Omur Baysal. Meta-analysis of gene expression in neurodegenerative diseases reveals patterns in gaba synthesis and heat stress pathways, 2019.

[19] Nan Zheng, Vincent Fitzpatrick, Ran Cheng, Linli Shi, David L. Kaplan, and Chen Yang. Photoacoustic silk scaffolds for neural stimulation and regeneration, 2021.

[20] Won Suk Lee, Won-Ha Lee, Yong Chul Bae, and Kyoungho Suk. Axon guidance molecules guiding neuroinflammation. *Experimental Neurobiology*, 28(3):311, 2019.

[21] Role of netrin-1 signaling in ne.

[22] Johannes Weickenmeier, Ellen Kuhl, and Alain Goriely. The multiphysics of prion-like diseases: progression and atrophy, 2018.

[23] Farzaneh Esmaili, Mahdi Pourmirzaei, Shahin Ramazi, Seyedehsamaneh Shojaeilangari, and Elham Yavari. A review of machine learning and algorithmic methods for protein phosphorylation sites prediction, 2022.

[24] Laura Pellegrini, Andrea Wetzel, Simone Grannó, George Heaton, and Kirsten Harvey. Back to the tubule: microtubule dynamics in parkinson's disease. *Cellular and Molecular Life Sciences*, 74:409–434, 2017.

[25] Kohei Nishida, Kosuke Matsumura, Miki Tamura, Takuto Nakamichi, Keiya Shimamori, Masahiro Kuragano, Arif Md Rashedul Kabir, Akira Kakugo, Susumu Kotani, Naoki Nishishita, et al. Effects of three microtubule-associated proteins (map2, map4, and tau) on microtubules' physical properties and neurite morphology. *Scientific Reports*, 13(1):8870, 2023.

[26] Brigette Y Monroy, Danielle L Sawyer, Bryce E Ackermann, Melissa M Borden, Tracy C Tan, and Kassandra M Ori-McKenney. Competition between microtubule-associated proteins directs motor transport. *Nature communications*, 9(1):1487, 2018.

[27] Article.

[28] Matthias Schmidt and Jan Kierfeld. Chemomechanical simulation of microtubule dynamics with explicit lateral bond dynamics, 2021.

[29] Amir Shee, Vidur Sabharwal, Sandhya P. Koushika, Amitabha Nandi, and Debasish Chaudhuri. Unc-104 transport properties are robust and independent of changes in its cargo binding, 2024.

[30] Björn Zelinski, Nina Müller, and Jan Kierfeld. Dynamics and length distribution of microtubules under force and confinement, 2012.

[31] Hideyuki Nakashima, Keita Tsujimura, Koichiro Irie, Masataka Ishizu, Miao Pan, Tomonori Kameda, and Kinichi Nakashima. Canonical tgf-β signaling negatively regulates neuronal morphogenesis through tgif/smad complex-mediated crmp2 suppression. *Journal of Neuroscience*, 38(20):4791–4810, 2018.

[32] Danko Dimchev Georgiev. Impairment of consciousness in alzheimer's disease: the amyloid water-filled nanotubes manifest quantum optical coherence interfering with the normal qbd?, 2002.

[33] Leanne M Holt, Raymundo D Hernandez, Natasha L Pacheco, Beatriz Torres Ceja, Muhannah Hossain, and Michelle L Olsen. Astrocyte morphogenesis is dependent on bdnf signaling via astrocytic trkb. t1. *Elife*, 8:e44667, 2019.

[34] Gizem Inak, Agnieszka Rybak-Wolf, Pawel Lisowski, Tancredi M Pentimalli, René Jüttner, Petar Glažar, Karan Uppal, Emanuela Bottani, Dario Brunetti, Christopher Secker, et al. Defective metabolic programming impairs early neuronal morphogenesis in neural cultures and an organoid model of leigh syndrome. *Nature Communications*, 12(1):1929, 2021.

[35] Eyal Karzbrun, Aimal H Khankhel, Heitor C Megale, Stella MK Glasauer, Yofiel Wyle, George Britton, Aryeh Warmflash, Kenneth S Kosik, Eric D Siggia, Boris I Shraiman, et al. Human neural tube morphogenesis in vitro by geometric constraints. *Nature*, 599(7884):268–272, 2021.

[36] Kuanren Qian, Ashlee S. Liao, Shixuan Gu, Victoria A. Webster-Wood, and Yongjie Jessica Zhang. Biomimetic iga neuron growth modeling with neurite morphometric features and cnn-based prediction, 2023.

[37] Carla G Silva, Elise Peyre, and Laurent Nguyen. Cell migration promotes dynamic cellular interactions to control cerebral cortex morphogenesis. *Nature Reviews Neuroscience*, 20(6):318–329, 2019.

[38] Gavin T Knight, Brady F Lundin, Nisha Iyer, Lydia MT Ashton, William A Sethares, Rebecca M Willett, and Randolph Scott Ashton. Engineering induction of singular neural rosette emergence within hpsc-derived tissues. *Elife*, 7:e37549, 2018.

[39] Kavita Shah and Sandra Rossie. Tale of the good and the bad cdk5: remodeling of the actin cytoskeleton in the brain. *Molecular neurobiology*, 55:3426–3438, 2018.

[40] Takamitsu Hattori and Shohei Koide. Next-generation antibodies for post-translational modifications. *Current opinion in structural biology*, 51:141–148, 2018.

[41] Ji Min Lee, Henrik M Hammarén, Mikhail M Savitski, and Sung Hee Baek. Control of protein stability by post-translational modifications. *Nature Communications*, 14(1):201, 2023.

[42] Pascale Barbier, Orgeta Zejneli, Marlène Martinho, Alessia Lasorsa, Valérie Belle, Caroline Smet-Nocca, Philipp O Tsvetkov, François Devred, and Isabelle Landrieu. Role of tau as a microtubule-associated protein: structural and functional aspects. *Frontiers in aging neuroscience*, 11:204, 2019.

[43] Dimitrios Tsikas. Post-translational modifications (ptm): analytical approaches, signaling, physiology and pathophysiology—part i. *Amino Acids*, 53(4):485–487, 2021.

[44] Clement Champion, Jasper Lamers, Victor Arnold Shivas Jones, Giulia Morieri, Suvi Honkanen, and Liam Dolan. Microtubule associated protein wave dampened2-like (wdl) controls microtubule bundling and the stability of the site of tip-growth in marchantia polymorpha rhizoids. *Plos Genetics*, 17(6):e1009533, 2021.

[45] Onsurang Wattanathamsan and Varisa Pongrakhananon. Emerging role of microtubule-associated proteins on cancer metastasis. *Frontiers in Pharmacology*, 13:935493, 2022.

[46] Ishtiaque Ahammad. Identification of key proteins involved in axon guidance related disorders: A systems biology approach, 2018.

[47] Saurabh Mahajan and Chaitanya A. Athale. Spatial and temporal sensing limits of microtubule polarization in neuronal growth cones by intracellular gradients and forces, 2012.

[48] JD Comer, S Alvarez, SJ Butler, and JA Kaltschmidt. Commissural axon guidance in the developing spinal cord: from cajal to the present day. *Neural Development*, 14:1–16, 2019.

[49] LaFreda J Howard, Haley E Brown, Benjamin C Wadsworth, and Timothy A Evans. Midline axon guidance in the drosophila embryonic central nervous system. In *Seminars in cell & developmental biology*, volume 85, pages 13–25. Elsevier, 2019.

[50] Rui Ponte Costa. Computational model of axon guidance, 2015.

[51] Cyril Addi, Jian Bai, and Arnaud Echard. Actin, microtubule, septin and escrt filament remodeling during late steps of cytokinesis. *Current opinion in cell biology*, 50:27–34, 2018.

[52] P. G. Kevrekidis, Travis Thompson, and Alain Goriely. Anisotropic diffusion and traveling waves of toxic proteins in neurodegenerative diseases, 2020.

[53] Zachary Gergely, Ammon Crapo, Loren E. Hough, J. Richard McIntosh, and Meredith D. Betterton. Kinesin-8 effects on mitotic microtubule dynamics contribute to spindle function in fission yeast, 2016.

[54] Georgia Rapti, Chang Li, Alan Shan, Yun Lu, and Shai Shaham. Glia initiate brain assembly through noncanonical chimaerin–furin axon guidance in c. elegans. *Nature neuroscience*, 20(10):1350–1360, 2017.

[55] Xiang-Ying Ji and Xi-Qiao Feng. Mechanochemical modeling of dynamic microtubule growth involving sheet-to-tube transition, 2011.

[56] Ranjith Padinhateeri, Anatoly B. Kolomeisky, and David Lacoste. The random release of phosphate controls the dynamic instability of microtubules, 2011.

[57] Lingling Wang, Ming Yan, Chris KC Wong, Renshan Ge, Xiaolong Wu, Fei Sun, and C Yan Cheng. Microtubule-associated proteins (maps) in microtubule cytoskeletal dynamics and spermatogenesis. 2021.

[58] Inês LS Delgado, João Gonçalves, Rita Fernandes, Sara Zúquete, Afonso P Basto, Alexandre Leitão, Helena Soares, and Sofia Nolasco. Balancing act: Tubulin glutamylation and microtubule dynamics in toxoplasma gondii. *Microorganisms*, 12(3):488, 2024.

[59] Charles E. McAnany and Cameron Mura. Claws, disorder, and conformational dynamics of the c-terminal region of human desmoplakin, 2016.

[60] Szymon W Manka and Carolyn A Moores. The role of tubulin–tubulin lattice contacts in the mechanism of microtubule dynamic instability. *Nature structural & molecular biology*, 25(7):607–615, 2018.

[61] Safura Rashid-Shomali and Ali Najafi. Microtubule dynamics and oscillating state for mitotic spindle, 2010.

[62] Patrick C Kerstein, Kevin M Patel, and Timothy M Gomez. Calpain-mediated proteolysis of talin and fak regulates adhesion dynamics necessary for axon guidance. *Journal of Neuroscience*, 37(6):1568–1580, 2017.

[63] Macarena Pavez, Adrian C Thompson, Hayden J Arnott, Camilla B Mitchell, Ilaria D'Atri, Emily K Don, John K Chilton, Ethan K Scott, John Y Lin, Kaylene M Young, et al. Stim1 is required for remodeling of the endoplasmic reticulum and microtubule cytoskeleton in steering growth cones. *Journal of Neuroscience*, 39(26):5095–5114, 2019.

[64] Y. Suleymanov, F. Gafarov, and N. Khusnutdinov. Modeling of interstitial branching of axonal networks, 2013.

[65] Louis Reese, Anna Melbinger, and Erwin Frey. Molecular mechanisms for microtubule length regulation by kinesin-8 and xmap215 proteins, 2014.

[66] Katrina C McNeely, Timothy D Cupp, Jessica Neville Little, Kerstin M Janisch, Ayushma Shrestha, and Noelle D Dwyer. Mutation of kinesin-6 kif20b causes defects in cortical neuron polarization and morphogenesis. *Neural Development*, 12:1–18, 2017.

[67] Georgia S. Brennan and Alain Goriely. A network aggregation model for the dynamics and treatment of neurodegenerative diseases at the brain scale, 2024.

[68] Murat Bilgel, Jerry L. Prince, Dean F. Wong, Susan M. Resnick, and Bruno M. Jedynak. A multivariate nonlinear mixed effects model for longitudinal image analysis: Application to amyloid imaging, 2016.

[69] Quentin Lo Giudice, Marion Leleu, Gioele La Manno, and Pierre J Fabre. Single-cell transcriptional logic of cell-fate specification and axon guidance in early-born retinal neurons. *Development*, 146(17):dev178103, 2019.

[70] Laura E McCormick and Stephanie L Gupton. Mechanistic advances in axon pathfinding. *Current opinion in cell biology*, 63:11–19, 2020.

[71] Aileen Roth, Adrian Gihring, Joachim Bischof, Leiling Pan, Franz Oswald, and Uwe Knippschild. Ck1 is a druggable regulator of microtubule dynamics and microtubule-associated processes. *Cancers*, 14(5):1345, 2022.

[72] Wen Li, Feifei Li, Xia Zhang, Hui-Kuan Lin, and Chuan Xu. Insights into the post-translational modification and its emerging role in shaping the tumor microenvironment. *Signal transduction and targeted therapy*, 6(1):422, 2021.

[73] Monika A Myszczynska, Poojitha N Ojamies, Alix MB Lacoste, Daniel Neil, Amir Saffari, Richard Mead, Guillaume M Hautbergue, Joanna D Holbrook, and Laura Ferraiuolo. Applications of machine learning to diagnosis and treatment of neurodegenerative diseases. *Nature reviews neurology*, 16(8):440–456, 2020.

[74] Bing Bai, David Vanderwall, Yuxin Li, Xusheng Wang, Suresh Poudel, Hong Wang, Kaushik Kumar Dey, Ping-Chung Chen, Ka Yang, and Junmin Peng. Proteomic landscape of alzheimer's disease: novel insights into pathogenesis and biomarker discovery. *Molecular neurodegeneration*, 16(1):55, 2021.

[75] Daniele Ravi, Daniel C. Alexander, and Neil P. Oxtoby. Degenerative adversarial neuroimage nets: Generating images that mimic disease progression, 2019.

[76] Paul P Partyka, Ying Jin, Julien Bouyer, Angelica DaSilva, George A Godsey, Robert G Nagele, Itzhak Fischer, and Peter A Galie. Harnessing neurovascular interaction to guide axon growth. *Scientific reports*, 9(1):2190, 2019.

Disclaimer:

SurveyX is an AI-powered system designed to automate the generation of surveys. While it aims to produce high-quality, coherent, and comprehensive surveys with accurate citations, the final output is derived from the AI's synthesis of pre-processed materials, which may contain limitations or inaccuracies. As such, the generated content should not be used for academic publication or formal submissions and must be independently reviewed and verified. The developers of SurveyX do not assume responsibility for any errors or consequences arising from the use of the generated surveys.