The Role of PP2A in the Pathological Mechanisms of Alzheimer's Disease and Advances in Its Therapeutic Applications

Ketong Qian
Dulwhich College Suzhou, Jiangsu, China

Keywords: Protein Phosphatase 2A (PP2A), Alzheimer's Disease, Therapeutic Target.

Abstract: Alzheimer's disease (AD), a neurodegenerative disorder of the central nervous system, has become a pressing global health concern. The increasing incidence of AD, driven by an aging population, imposes significant socioeconomic burdens. Despite decades of research, the exact etiology and molecular mechanisms of AD remain unclear, limiting the development of effective treatments. It regulates key processes such as cell cycle progression, apoptosis, and signal transduction. Recent studies highlight its crucial role in AD pathophysiology, particularly in tau dephosphorylation and Aβ metabolism. Dysfunctional PP2A activity has been implicated in tau hyperphosphorylation, a major contributor to neurofibrillary tangle formation, and in the dysregulation of Aβ clearance. Investigating the role of PP2A in AD pathogenesis provides valuable insights into disease mechanisms and potential therapeutic targets. This review discusses the structural and functional aspects of PP2A, its contribution to AD pathology, and emerging therapeutic strategies aimed at modulating PP2A activity. Understanding these aspects may lead to the development of innovative approaches for early diagnosis, precision medicine, and disease prevention, ultimately improving patient outcomes.

1 INTRODUCTION

Alzheimer's disease (AD), a neurodegenerative disorder of the central nervous system, has become a growing global health challenge (Benmelouka, et al., 2022). With accelerated population aging worldwide, the incidence of AD has risen significantly, imposing heavy burdens on families and societies.

The primary pathological features of AD include extracellular β-amyloid (Aβ) plaques, intracellular neurofibrillary tangles (NFTs) caused by hyperphosphorylation of tau protein, neuronal loss, and synaptic dysfunction. Despite decades of research into AD pathogenesis, its exact etiology and mechanisms remain unclear, resulting in limited effective treatments (Tiwari, et al., 2019).

Protein phosphatase 2A (PP2A), a ubiquitously expressed serine/threonine phosphatase with critical biological functions, regulates diverse cellular processes, including cell cycle progression, proliferation, differentiation, and apoptosis (Swerdlow, et al., 2023). Recent studies highlight PP2A's pivotal role in AD pathophysiology.

In-depth investigation of PP2A's role in AD pathogenesis will not only advance our understanding of the disease but also provide novel theoretical insights and potential therapeutic targets. Elucidating the relationship between PP2A and AD pathology may enable interventions to modulate PP2A activity, offering new avenues for early diagnosis, precision therapy, and disease prevention. Thus, systematic research on PP2A's role in AD mechanisms and its therapeutic applications holds profound scientific and practical significance.

2 STRUCTURAL AND FUNCTIONAL BASIS OF PP2A

2.1 Molecular Architecture of PP2A

PP2A is a heterotrimeric enzyme composed of a structural subunit A (scaffold), a catalytic subunit C, and a regulatory subunit B. Subunit A, characterized by its helical repeat structure, provides a platform for binding subunits B and C, ensuring structural stability (Dentoni, et al., 2022). Subunit C contains a conserved catalytic site essential for phosphatase

Qian, K.
The Role of PP2A in the Pathological Mechanisms of Alzheimer's Disease and Advances in Its Therapeutic Applications.
DOI: 10.5220/0014436900004933

In *Proceedings of the 1st International Conference on Biomedical Engineering and Food Science (BEFS 2025)*, pages 149-154
ISBN: 978-989-758-789-4

activity, while regulatory B subunits confer substrate specificity and subcellular localization.

2. Structure and Functional Basis of PP2A

2.2 Review of Molecular Structure Studies on PP2A

PP2A, as a protein phosphatase that plays a critical role in cellular physiological processes, has been a major focus of research in this field. A deeper understanding of the molecular structure of PP2A is essential for elucidating its mechanisms in normal physiological functions and disease development.

Structural subunit A, also known as subunit A, features a unique double-helical repeat structure that provides a binding platform for catalytic subunit C and regulatory subunit B, playing an indispensable role in maintaining the overall structural stability of the PP2A holoenzyme (Dentoni, et al., 2022). This double-helical repeat structure organizes the subunits in an orderly manner, ensuring proper interactions among them and thereby supporting the normal function of the PP2A holoenzyme.

Catalytic subunit C is the core component responsible for the phosphatase activity of PP2A. Its structure contains multiple functional regions that precisely regulate catalytic activity. The active site of catalytic subunit C is highly conserved and can specifically recognize and bind phosphate groups on substrates, removing them through hydrolysis to regulate the phosphorylation state of substrate proteins. Studies have shown that even minor changes in the active site of catalytic subunit C can significantly affect the catalytic activity of PP2A, thereby influencing the normal operation of numerous intracellular signaling pathways.

Regulatory subunit B exhibits diversity, with different types of regulatory subunits B conferring distinct substrate specificity and intracellular localization to the PP2A holoenzyme. By interacting with structural subunit A and catalytic subunit C, regulatory subunit B finely tunes the affinity of the PP2A holoenzyme for specific substrates and its catalytic activity. Different regulatory subunits B are expressed at varying levels in different tissues and cell types, enabling PP2A to perform diverse functions under various physiological and pathological conditions.

In recent years, these techniques have provided powerful tools for understanding the subunit composition, subunit interactions, and three-dimensional structure of the PP2A holoenzyme. Through these studies, the understanding of the molecular structure of PP2A has deepened, laying a solid foundation for further exploration of its functions in physiological and pathological processes.

2.3 Research on the Normal Physiological Functions of PP2A

PP2A, as a phosphatase in cellular physiological processes, has broad and complex normal physiological functions. These functions are essential for maintaining intracellular homeostasis.

In the regulation of cellular signal transduction, PP2A acts as a precise "regulator." The accurate operation of numerous intracellular signaling pathways relies on the dynamic balance between protein phosphorylation and dephosphorylation. PP2A can specifically remove phosphate groups from certain proteins, thereby terminating or modulating signal transmission (Del, et al., 2017). For example, in growth factor signaling pathways, when cells receive growth factor stimulation, a series of proteins undergo phosphorylation and activation, promoting signal transmission related to cell growth and proliferation. PP2A plays a timely role by dephosphorylating these activated proteins, preventing excessive signal activation and ensuring that cell growth and proliferation remain within normal regulatory limits, thereby avoiding abnormal cell proliferation and diseases such as cancer.

The normal progression of the cell cycle also depends on the fine regulation of PP2A. The cell cycle is a highly ordered process involving strict regulation at multiple key checkpoints. PP2A plays different roles at various stages of the cell cycle. During the G1 phase, it participates in regulating the activity of cyclin-dependent kinase (CDK) complexes, influencing whether cells enter the S phase for DNA replication. During mitosis, PP2A is indispensable for spindle assembly and proper chromosome separation. By regulating the phosphorylation state of related proteins, PP2A ensures the correct connection between spindle microtubules and chromosomes and the accurate separation of sister chromatids, guaranteeing the precision and stability of cell division.

Additionally, PP2A plays a crucial role in maintaining cytoskeletal stability. The cytoskeleton is a network of protein fibers within cells that is essential for maintaining cell shape, movement, and intracellular transport. PP2A regulates the phosphorylation levels of cytoskeleton-related proteins, influencing the dynamic balance between

cytoskeletal assembly and disassembly (Reddy et al., 2011). When cells undergo morphological changes or migration in response to external stimuli, PP2A can promptly adjust the phosphorylation state of cytoskeleton-related proteins, facilitating cytoskeletal remodeling to meet cellular physiological needs.

In summary, the normal physiological functions of PP2A broadly encompass cellular signal transduction, cell cycle regulation, and cytoskeletal stability, among other critical aspects. These functions work together to maintain the normal physiological state of cells and organisms. A deeper understanding of the normal physiological functions of PP2A provides a solid foundation for further exploration of its role in disease development.

3 RESEARCH ON THE ROLE OF PP2A IN THE PATHOLOGICAL MECHANISMS OF AD

3.1 Review of the Relationship between PP2A and Aβ Protein Metabolism

The relationship between PP2A and Aβ protein metabolism is a key aspect of understanding the pathological mechanisms of AD. The abnormal metabolism of Aβ protein plays a central role in the pathogenesis of AD, and the role of PP2A in this process has become a focus of research.

In terms of Aβ production, abnormal processing of the amyloid precursor protein (APP) is a major cause of increased Aβ generation. PP2A can regulate the activity of related proteases, influencing the cleavage process of APP (Patro, et al., 2021). Some studies have found that when PP2A activity is reduced, particularly the neurotoxic Aβ42. This process involves complex cellular signaling pathways and molecular interaction networks, with PP2A as a key regulatory factor. Dysfunction of PP2A may disrupt the normal balance of APP processing, leading to excessive Aβ production.

In terms of Aβ aggregation, PP2A also has a significant impact. The aggregation of Aβ into oligomers and fibrillar deposits is one of the neuropathological features of AD. Research indicates that PP2A can interact with Aβ, influencing its aggregation kinetics. When PP2A functions normally, it may inhibit Aβ aggregation, reducing the formation of oligomers and fibrils. However, when PP2A activity is inhibited or its expression is abnormal, Aβ is more prone to aggregate, forming neurotoxic structures that impair neuronal function.

Furthermore, PP2A plays a role in the clearance of Aβ protein. Under normal conditions, the body has multiple mechanisms for clearing Aβ, including transport across the blood-brain barrier and phagocytosis by microglia. PP2A can regulate related intracellular signaling pathways, affecting the phagocytic ability of microglia and the transport function of the blood-brain barrier. When PP2A function is impaired, the efficiency of Aβ clearance may decrease, leading to its accumulation in the brain and exacerbating neuropathological damage.

In conclusion, PP2A is closely related to Aβ protein metabolism. In-depth research on the relationship between PP2A and Aβ protein metabolism will help further elucidate the pathogenesis of AD and provide a theoretical basis for developing therapeutic strategies targeting abnormal Aβ metabolism. Future studies should further clarify the specific molecular mechanisms of PP2A in various aspects of Aβ metabolism and explore how to modulate PP2A function to intervene in abnormal Aβ metabolism, thereby opening new avenues for AD treatment.

3.2 Research on the Relationship between PP2A and Tau Protein Hyperphosphorylation

In the pathological mechanisms of AD, the hyperphosphorylation of tau protein plays a critical role, and there is a complex and close relationship between PP2A and tau protein hyperphosphorylation.

Tau protein plays a crucial role in maintaining the normal structure and function of neurons. However, in the brains of AD patients, tau protein becomes excessively phosphorylated, forming neurofibrillary tangles (NFTs), which are a key pathological feature of AD (Leal, et al., 2020). The accumulation of NFTs disrupts the cytoskeletal structure within neurons, leading to neuronal dysfunction and death, and ultimately contributing to cognitive decline.

PP2A plays a key role in regulating the phosphorylation levels of various intracellular proteins, including tau protein. Studies have shown that changes in PP2A activity are closely related to tau protein hyperphosphorylation. Under normal physiological conditions, PP2A can promptly remove excess phosphate groups from tau protein, maintaining the dynamic balance.

However, in the brain tissues of AD patients, PP2A activity is significantly reduced. Various

factors can lead to decreased PP2A activity, such as the upregulation of endogenous PP2A inhibitors in the brains of AD patients, which bind to and inhibit PP2A, reducing its ability to dephosphorylate tau protein and resulting in tau hyperphosphorylation. Additionally, pathological processes such as oxidative stress may also affect the structure and function of PP2A, further reducing its activity.

At the same time, hyperphosphorylated tau protein may, in turn, affect PP2A. Overly phosphorylated tau protein may interfere with the subcellular localization of PP2A or affect its interactions with other regulatory proteins, further disrupting the normal function of PP2A and creating a vicious cycle.

In-depth research on the relationship between PP2A and tau protein hyperphosphorylation will help us better understand the pathogenesis of AD. This not only provides new perspectives for elucidating the pathological processes of AD but also offers potential targets for developing therapeutic strategies. By modulating PP2A activity, it may be possible to correct tau protein hyperphosphorylation, thereby delaying or preventing the progression of AD, which has significant theoretical and clinical implications for AD treatment.

4 ADVANCES IN PP2A-BASED AD THERAPEUTIC APPLICATIONS

4.1 Review of Drug Development Targeting PP2A

Drug development targeting PP2A has garnered significant attention in the field of AD treatment. As research into the pathological mechanisms of AD deepens, PP2A has emerged as a key regulatory molecule and a promising drug target.

In recent years, numerous research teams have focused on developing drugs targeting PP2A. Some studies have concentrated on small-molecule compounds, aiming to precisely modulate PP2A activity to intervene in the pathological processes of AD (Markovinovic, et al., 2022). These small-molecule drugs can specifically bind to certain structural domains of PP2A, altering its conformation and thereby affecting its interactions with substrates, ultimately regulating related signaling pathways. For example, some small-molecule drugs can enhance PP2A's dephosphorylation of tau protein.

At the same time, natural products and their derivatives have become an important source of drug development targeting PP2A. Many plant extracts contain components with potential PP2A-modulating activity. Through isolation, identification, and structural modification, these components hold promise for developing novel AD treatments. Certain flavonoids have been found to activate PP2A, improving Aβ protein metabolism and reducing Aβ amyloid plaque deposition, offering new approaches for AD treatment.

In the field of antibody drug development, progress has also been made. By generating monoclonal antibodies targeting specific epitopes of PP2A, its function in vivo can be precisely regulated. These antibodies can specifically block PP2A's interactions with certain pathogenic factors or enhance its binding to beneficial regulatory molecules, thereby exerting therapeutic effects.

However, drug development targeting PP2A is not without challenges. PP2A is involved in numerous physiological processes within cells, and excessive or inappropriate modulation of its activity may lead to a range of side effects. Therefore, achieving precise regulation of PP2A activity to effectively treat AD while avoiding adverse effects is a major challenge. Additionally, issues such as the pharmacokinetic properties of drugs and their ability to cross the blood-brain barrier require further research and optimization. Despite these challenges, drug development targeting PP2A offers new hope for AD treatment. With continuous technological advancements and deeper research, safer and more effective therapeutic drugs may be developed, bringing benefits to AD patients.

4.2 Research on the Application of PP2A as a Diagnostic Biomarker for AD

In the early diagnosis and monitoring of AD, identifying effective diagnostic biomarkers is crucial. PP2A, as a protein phosphatase that plays a critical role in cellular physiological processes, has recently gained attention in research on its application as a diagnostic biomarker for AD (Wong, et al., 2017).

Multiple studies have shown that PP2A exhibits different expression patterns and activity changes in the brain tissues and body fluids of AD patients compared to healthy individuals. In brain tissues, techniques such as immunohistochemistry and Western blotting have revealed significantly reduced PP2A protein levels and activity in specific regions of

AD patients' brains, such as the hippocampus and temporal cortex. These changes are closely associated with the formation of AD neuropathological features like Aβ plaques and tau protein tangles. This suggests that changes in PP2A levels and activity may be involved, making it a potential diagnostic biomarker.

In body fluids, blood and cerebrospinal fluid (CSF) are the primary focuses of research. Analysis of blood samples from AD patients has shown that plasma levels of PP2A-related protein subunits are associated with disease severity. As the disease progresses, the levels of certain PP2A subunits undergo significant changes, offering the possibility of early AD screening through blood tests. In CSF studies, differences in PP2A activity and related metabolite concentrations have been observed between AD patients and healthy controls. These differences can appear, serving as sensitive indicators for early AD diagnosis.

Additionally, the PP2A is also reflected in its combined use with other known diagnostic markers. When used alongside traditional markers like Aβ42 and tau protein, PP2A-related indicators can improve the accuracy and specificity of AD diagnosis (Schuiki et al., 2009). By constructing multi-marker diagnostic models, a more comprehensive assessment of an individual's risk of developing AD can be achieved, providing stronger support for clinical diagnosis and disease evaluation.

However, challenges remain in using PP2A as a diagnostic biomarker for AD (Yeo, et al., 2021). For example, differences in detection methods and sample sources across studies have led to heterogeneity in results, necessitating the standardization of detection methods and sample collection procedures. Additionally, the mechanisms underlying the dynamic changes of PP2A during AD development require further research to better understand its biological basis as a diagnostic biomarker. Despite these challenges, the potential of PP2A as a diagnostic biomarker offers new directions for the early diagnosis and intervention of AD. With continued research, breakthroughs in AD diagnosis may be achieved.

5 CONCLUSION

In the field of PP2A and AD research, numerous scholars have conducted extensive and fruitful work, providing a solid foundation for a deeper understanding of PP2A's role in AD pathological mechanisms and its applications.

In terms of the structure and functional basis of PP2A, research on its molecular structure has been thorough, clearly revealing the unique composition and architecture of PP2A. This has laid the groundwork for further exploration of its functions in physiological and pathological states. Progress has been adopted in studying the normal physiological functions of PP2A, clarifying its indispensable role in key processes such as cellular signal transduction and metabolic regulation.

Regarding the role of PP2A in AD pathological mechanisms, research on the relationship between PP2A and Aβ protein metabolism has yielded substantial results. Numerous studies have shown that changes in PP2A activity are closely related to the production, aggregation, and clearance of Aβ protein, providing new perspectives for understanding abnormal Aβ metabolism in AD pathogenesis. Important breakthroughs have also been made in research on the relationship between PP2A and tau protein hyperphosphorylation, revealing that PP2A activity imbalance may be a key factor leading to tau protein hyperphosphorylation.

In the application of PP2A-based AD treatments, research on drug development targeting PP2A is actively advancing. Many studies are focused on screening and developing drug molecules that can modulate PP2A activity, with some drugs showing therapeutic potential in animal experiments. Additionally, new discoveries have been made in the application of PP2A as a diagnostic biomarker for AD, with changes in its expression levels in blood or CSF holding promise for the diagnosis and intervention.

However, despite the achievements of existing research, there are still some limitations. Future research should further explore the complex molecular regulatory networks of PP2A in AD pathogenesis, strengthen interdisciplinary research, improve the success rate of PP2A-targeted drug development, and validate the clinical value of PP2A as a diagnostic biomarker. Through these efforts, new breakthroughs in AD treatment and diagnosis may be achieved.

REFERENCES

Benmelouka, A. Y., Ouerdane, Y., Outani, O., et al. 2022. Alzheimer's disease-related psychosis: An overview of clinical manifestations, pathogenesis, and current treatment. Current Alzheimer Research, 19(4), 285-301.

Del Prete, D., Suski, J. M., Oulès, B., et al. 2017. Localization and processing of the amyloid-β protein precursor in mitochondria-associated membranes. Journal of Alzheimer's Disease, 55(4), 1549-1570.

Dentoni, G., Castro-Aldrete, L., Naia, L., et al. 2022. The potential of small molecules to modulate the mitochondria–endoplasmic reticulum interplay in Alzheimer's disease. Frontiers in Cell and Developmental Biology, 10, 920228.

H. Reddy, P., & P. Reddy, T. 2011. Mitochondria as a therapeutic target for aging and neurodegenerative diseases. Current Alzheimer Research, 8(4), 393-409.

Leal, N. S., Dentoni, G., Schreiner, B., et al. 2020. Amyloid B-peptide increases mitochondria-endoplasmic reticulum contact altering mitochondrial function and autophagosome formation in Alzheimer's disease-related models. Cells, 9(12), 2552.

Markovinovic, A., Greig, J., Martín-Guerrero, S. M., et al. 2022. Endoplasmic reticulum–mitochondria signaling in neurons and neurodegenerative diseases. Journal of Cell Science, 135(3), jcs248534.

Patro, S., Ratna, S., Yamamoto, H. A., et al. 2021. ATP synthase and mitochondrial bioenergetics dysfunction in Alzheimer's disease. International Journal of Molecular Sciences, 22(20), 11185.

Schuiki, I., & Daum, G. 2009. Phosphatidylserine decarboxylases, key enzymes of lipid metabolism. IUBMB Life, 61(2), 151-162.

Swerdlow, R. H. 2023. The Alzheimer's disease mitochondrial cascade hypothesis: A current overview. Journal of Alzheimer's Disease, 92(3), 751-768.

Tiwari, S., Atluri, V., Kaushik, A., et al. 2019. Alzheimer's disease: Pathogenesis, diagnostics, and therapeutics. International Journal of Nanomedicine, 5541-5554.

Wong, M. W., Braidy, N., Poljak, A., et al. 2017. The application of lipidomics to biomarker research and pathomechanisms in Alzheimer's disease. Current Opinion in Psychiatry, 30(2), 136-144.

Yeo, H. K., Park, T. H., Kim, H. Y., et al. 2021. Phospholipid transfer function of PTPIP51 at mitochondria-associated ER membranes. EMBO Reports, 22(6), e51323.