SELECTIVE KINASE INHIBITOR FOR THE TREATMENT OF NEURODEGENERATIVE DISORDERS

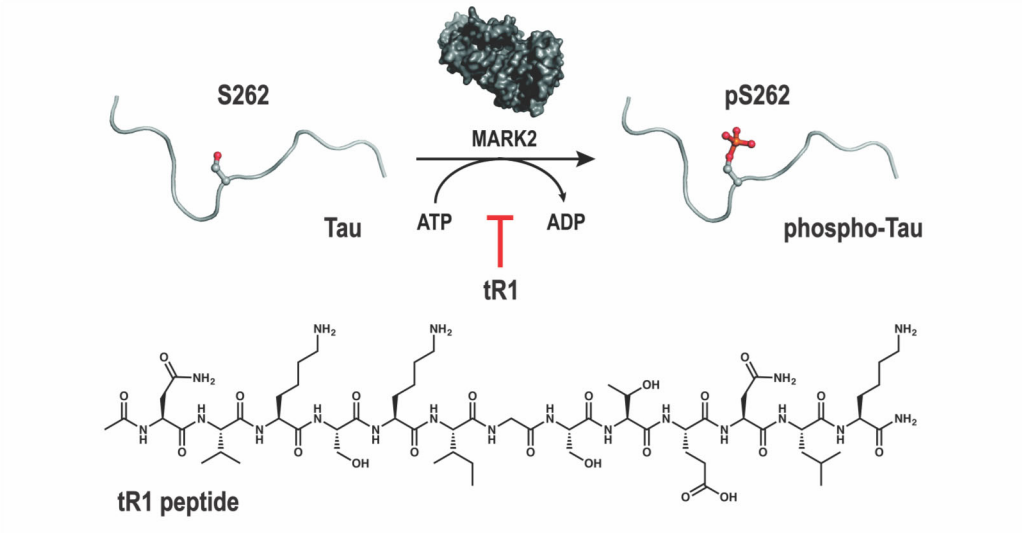
OU ID: #17027

Overview

The human genome encodes more than 500 unique protein kinases, making them one of the largest superfamilies of signaling proteins. Protein kinases perform many diverse functions within the cell and serve to regulate a broad range of essential metabolic processes including signal transduction, protein activation, transport and secretion. Given their profound influence on cell biology, it is perhaps not surprising that aberrant or dysregulated kinase activity can lead to the onset of various diseases such as diabetes, inflammation, cancer and neurodegeneration. Protein kinases are therefore widely considered attractive targets for therapeutic intervention. Unfortunately, high structural similarity among protein kinases makes selectively targeting discrete kinases a considerable challenge.

MARK2 is a serine/threonine protein kinase that phosphorylates the microtubule-associated protein tau. The tau protein is involved in facilitating the assembly, maintenance and stability of microtubules, which provide structure and stability to cells. Unfortunately, dysfunctional MARK2 activity often leads to hyperphosphorylated tau isoforms that can aggregate into higher order filaments known as neurofibrillary tangles (NFTs). If left untreated, NFTs can compromise the structural integrity of neurons, leading to the onset of neurodegenerative disorders such as Alzheimer's Disease and frontotemporal dementia.

Researchers at Ohio University have recently developed a synthetic peptide capable of selectively inhibiting the MARK2-mediated phosphorylation of tau. This 13 residue peptide, known as tR1, is a direct sequence mimic of the tau protein and inhibits tau phosphorylation at Ser262 in vitro and in cultured primary cortical neurons.



Benefits

By developing tR1 as a direct sequence mimic of the human tau repeat R1 domain, this novel peptide is able to selectively target and inhibit the MARK2-mediated phosphorylation of tau. Importantly, this inhibition is specific to MARK2, as tR1 does not inhibit other kinases that phosphorylate tau including GSK3b, CDK2 or CDK5. These results represent the first step in the development of next-generation peptide-based therapeutics designed to treat neurodegenerative disorders such as Alzheimer's disease and frontotemporal dementia.

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Commercial Application

Alzheimer's disease is currently the 6th leading cause of death in the United States and the 5th leading cause of death for individuals over the age of 65. According to the United States Alzheimer's Association, there are currently more than 5 million Americans over the age of 65 living with Alzheimer's disease. This number is expected to increase significantly as the U.S. population ages. Total payments for care and treatment of patients with Alzheimer's disease and other dementias are estimated to exceed $305 billion for 2020[1]. A new treatment option will not only alleviate some of the costs associated with the care of these patients, but will also improve the quality of life for those individuals suffering from these debilitating conditions.

Patent Status

U.S. Non-Provisional Patent Application filed October 15, 2019.

About the Inventor

Justin M. Holub, Ph.D. is an Associate Professor in the Department of Chemistry and Biochemistry at Ohio University. Dr. Holub received his Ph.D. from New York University in 2009 and completed his post-doctoral training at Yale University in 2013. Research in Dr. Holub's laboratory focuses on the development of chemical tools such as synthetic biologics and pro-fluorescent ligands to study and manipulate protein-protein interactions. To facilitate these studies, researchers in the Holub laboratory use multidisciplinary approaches to design molecules that target the interfacial contacts between proteins. His research has led to the discovery of novel peptides and miniature proteins that inhibit therapeutically-relevant protein-protein interactions, thus helping to expand the 'druggable' proteome.

Robert Colvin, Ph.D. is Professor and Chair for the Department of Biology at Ohio University. Dr. Colvin received his Ph.D. in cell physiology from Rutgers University. As a post-doctoral fellow in cardiology at the University of Connecticut, Dr. Colvin was at the forefront of research on the then newly discovered cardiac Na^+/Ca^{2+} exchanger and its role in cardiac disease. Upon completion of his post-doctoral training, Dr. Colvin focused his independent research on studying neurodegenerative diseases, specifically Alzheimer's disease and stroke. His current research involves evaluating the neuronal mechanisms of zinc homeostasis - in particular, discovering the cellular mechanisms that are responsible for buffering cytosolic free zinc concentrations and those involved in the control and regulation of cytosolic zinc transients. This knowledge is important for providing a better understanding of the underlying mechanisms of neural degeneration in diseases such as stroke and Alzheimer's disease.

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References

[1] Alzheimer's Disease Facts and Figures

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