Role of CRMP2 Interaction With Kinase CDK5 in Forming the Neurofibrillary Tangles of Alzheimer's Disease

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Alzheimer’s disease is an irreversible and fatal form of dementia caused by the degeneration of neurons in the brain. This disorder is characterized by the aggregation of tau protein, the structural stabilizer of brain cells, into insoluble fibrils within neurons. Normal Tau is regulated through phosphorylation by several kinases, including cyclin-dependent kinase 5 (CDK5). Aberrations in CDK5 function may be caused by binding with other proteins, such as collapsin response mediator protein 2 (CRMP2), a scaffolding protein found abundantly in neurons to modulate neurotransmitter release. How CRMP2 affects kinase CDK5 to influence the formation of neurofibrillary tau tangles is presently unknown. I hypothesized that CRMP2 interaction with CDK5 would result in the dysfunctional phosphorylation of tau, leading to tau fibrils. Therefore, I investigated the interaction between CRMP2 and CDK5 and its role in the formation of neurofibrillary tau tangles associated with Alzheimer’s disease. To examine the mechanism of interaction between CDK5 and CRMP2, I performed microscale thermophoresis (MST) and kinase assays. The results revealed that CRMP2 significantly inhibited CDK5's kinase activity by binding directly to form a complex. Mass spectroscopy proteomics showed that the CRMP2 binding significantly mitigated CDK5’s phosphorylation of tau at 8 sites. Finally, microplate photometry assays showed that the CRMP2-CDK5 complex resulted in the development of tau tangles. This data suggests that the interaction between CRMP2 and kinase CDK5 is a critical factor in forming the neurofibrillary tangles of Alzheimer’s disease, laying the groundwork for novel approaches that treat Alzheimer's disease.

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