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CNKSR2 interactome analysis indicates its association with the centrosome/ microtubule system

Abstract:

The protein Connector Enhancer of Kinase Suppressor of Ras 2 (CNKSR2), present in both the postsynaptic density and cytoplasm of neurons, is a scaffolding protein with several protein-binding domains. Variants of the CNKSR2 gene have been implicated in neurodevelopmental disorders, particularly intellectual disability, although the precise mechanism involved has not yet been fully understood. Research has demonstrated that CNKSR2 plays a role in facilitating the localization of postsynaptic density protein complexes to the membrane, thereby influencing synaptic signaling and the morphogenesis of dendritic spines. However, the function of CNKSR2 in the cytoplasm remains to be elucidated. In this study, we used immunoprecipitation and high-resolution liquid chromatography-mass spectrometry to identify the interactors of CNKSR2. Through a combination of bioinformatic analysis and cytological experiments, we found that the CNKSR2 interactors were significantly enriched in the proteome of the centrosome. We also showed that CNKSR2 interacted with the microtubule protein DYNC1H1 and with the centrosome marker CEP290. Subsequent colocalization analysis confirmed the centrosomal localization of CNKSR2. When we downregulated CNKSR2 expression in mouse neuroblastoma cells (Neuro 2A), we observed significant changes in the expression of numerous centrosomal genes. This manipulation also affected centrosome-related functions, including cell size and shape, cell proliferation, and motility. Furthermore, we found that CNKSR2 interactors were highly enriched in de novo variants associated with intellectual disability and autism spectrum disorder. Our findings establish a connection between CNKSR2 and the centrosome, and offer new insights into the underlying mechanisms of neurodevelopmental disorders.

Biography

Jing Li completed her PhD at the age of 27 from the Graduate School of the Chinese Academy of Sciences and conducted postdoctoral studies at the Zilkha Neurogenetic Institute, University of Southern California. She is an associate professor at the Institute for Translational Medicine, Qingdao University. She researches protein complexes associated with neurodevelopmental disorders. She has published over 20 papers in reputable journals and serves as a reviewer for several academic journals.