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A protein implicated in non-syndromic mental retardation regulates the camp/ protein kinase A (PKA) signaling pathway

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A mutation of the Coiled-coil and C2 domain containing 1A (CC2D1A) gene, which encodes a C2 domain and DM14 domain containing protein, has been linked to severe autosomal recessive non-syndromic mental retardation (NSMR). Using a mouse model that produces a truncated form of CC2D1A that lacks the C2 domain and three of the four DM14 domains, we found that CC2D1A is important for neuronal differentiation and brain development. CC2D1A mutant neurons are hypersensitive to stress and have a reduced capacity to form dendrites and synapses in culture. At the biochemical level, CC2D1A transduces signals to the cyclic adenosine 3', 5'-monophosphate (camp)-protein kinase A (PKA) pathway during neuronal cell differentiation. PKA activity is compromised and the translocation of its catalytic subunit to the nucleus is also defective in CC2D1A mutant cells. Consistently, phosphorylation of the PKA target cAMP responsive element binding protein (CREB), at serine 133, is nearly abolished in CC2D1A mutant cells. The defects in cAMP/PKA signaling were observed in fibroblast, macrophage and neuronal primary cells derived from the CC2D1A KO mice. CC2D1A associates with the cAMP/PKA complex following forskolin treatment, and accumulates in vesicles or on the plasma membrane in wild-type cells, suggesting that CC2D1A may recruit the PKA complex to the membrane to facilitate signal transduction. Moreover, CC2D1A associates constitutively bind PDE4D inhibiting its activity. Together, our data unravel that CC2D1A is an important regulator of the cAMP/PKA signaling pathway, which may be underlying causes for impaired mental function in NSMR patients with CC2D1A mutation.

Biography

Azza Altawashi has completed her Ph.D from Baylor College of Medicine, Houston, Texas and postdoctoral studies from Retinoblastoma Cancer Center, Texas Children's Hospital, Feigin center. He has published several papers in reputed journals.

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