CC2D1A deficiency disorders: autism spectrum disorder and cognitive dysfunction

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Coiled-coil and C2 domain containing 1A (CC2D1A) is an evolutionarily conserved protein, originally identified as a nuclear factor-κB activator through a large-scale screen of human genes. Mutations in the human *Cc2d1a* gene result in autosomal recessive nonsyndromic intellectual disability. It remains unclear, however, how *Cc2d1a* mutation leads to alterations in brain function. In this talk, I will discuss the current findings in our lab showing that how conditional deletion of *Cc2d1a* results in cognitive dysfunction and autism spectrum disorder (ASD). Taking advantage of *Cc2d1a* cKO mice, our study highlights the importance of CC2D1A in the maintenance of LTP at Schaffer collateral-CA1 synapses and the formation of hippocampus-dependent long-term object location memory. Our findings also established a critical link between elevated Rac1 activity, structural and synaptic plasticity alterations and cognitive impairment caused by *Cc2d1a* deletion. Moreover, partial blockade of Rac1 activity rescues synaptic plasticity and memory deficits in *Cc2d1a* cKO mice. We also found that CC2D1A deletion leads to a trend toward decreased number of cortical progenitor cells at embryonic day 12.5 and alters the cortical thickness on postnatal day 10. In addition, *Cc2d1a* cKO mice display autistic-like phenotypes including self-injurious repetitive grooming and aberrant social interactions. Loss of CC2D1A also results in decreased complexity of apical dendritic arbors of medial prefrontal cortex (mPFC) layer V pyramidal neurons and increased synaptic excitation/inhibition (E/I) ratio in the mPFC. Notably, chronic treatment with minocycline rescues behavioral and morphological abnormalities, as well as E/I changes, in male *Cc2d1a* cKO mice. Altogether, our results implicate Rac1 hyperactivity in synaptic plasticity and cognitive deficits observed in *Cc2d1a* cKO mice. Our findings also indicate that *Cc2d1a* cKO mice recapitulate autistic-like phenotypes of human disorder, and suggest that minocycline has both structural and functional benefits in treating ASD.

References

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