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β-catenin networks as a new molecular target in infantile spasms and seizures

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Infantile Spasms (IS) constitute a devastating childhood epilepsy syndrome. Effective treatments are largely lacking because Infantile Syndrome is molecularly ill-defined. Using genetic manipulations in mice, we show here that deregulation of β-catenin networks leads to characteristics of human IS. We conditionally deleted the Adenomatous Polyposis Coli Gene (APC cKO) or conditionally overexpressed β-catenin (β-cat cOE). APC is a major negative regulator of β-cat levels. β-cat has dual roles in cadherin synaptic adhesion complexes and the canonical Wnt pathway both are critical for normal brain circuit formation and function. APC cKO and β-cat cOE mice both display high amplitude spastic movements at neonatal ages and spontaneous seizures at adult ages compared with control littermates. They also exhibit cognitive and autism-like disabilities known co-morbidities of human IS. EEG recordings show abnormal cortical circuit activity and seizures. Cortical hyper-excitability is suggested by increased spontaneous and evoked excitatory electrical activity and increased synaptic spine density in cortical layer 5 pyramidal neurons. β-cat protein levels are elevated as are canonical Wnt target gene expression and β-cat association with N-cadherin suggesting altered synaptic stability and plasticity. We identify APC cKO and β-cat cOE mice as new models of IS. We propose a novel molecular etiology of IS that is centered on aberrant β-cat networks. As further support, several genes implicated in human IS (ARX, FoxG1, TSC1/2 and Magi2/S-SCAM) are predicted to affect β-cat and its associated pathways. Defining new molecular targets is essential for developing new and effective interventions to ameliorate IS.

Biography

Michele Jacob has obtained her PhD from Yale University and conducted Postdoctoral studies at Columbia University and the University of California, San Diego. She had an independent research lab at the Worcester Foundation for Biomedical Research and moved to Tufts University in 1997. She has published 48 papers and serves as a Reviewing Editor for *Frontiers in Synaptic Neuroscience*. Her studies are defining molecular mechanisms in vivo that are critical for the proper maturation and function of neuronal and sensory cell synapses. She is also identifying mechanisms responsible for synaptic dysfunction in autism, intellectual disabilities, hearing loss and infantile spasms/seizures.

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