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EPIGENETIC MECHANISMS IN NEURAL STEM CELLS AND MENTAL HEALTH

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Epigenetics regulate gene expression and brain development through mechanisms that are not directly controlled by the genetic DNA sequences. Recent discoveries have highlighted the importance of epigenetic mechanisms in brain development, stem cell differentiation, and mental health. MeCP2 is an important epigenetic factor in the brain and its mutation or altered expression leads to impaired brain development and function. Rett Syndrome is a severe neurodevelopmental disorder that is caused by *MECP2* mutations and has no cure. These patients seem to be normal at birth, but within the first 2 years of age, they display developmental regression, mental disability, neurological symptoms, seizers, speech deficiencies, irregular breathing, anxiety, and autism. It is well established that impaired protein translation is a characteristic of human Rett Syndrome neurons. However, the underlying molecular mechanism of this phenotype is poorly understood. To study Rett Syndrome pathobiology, my lab investigates the role of individual MeCP2 isoforms in controlling fundamental molecular pathways aiming to explain how MeCP2 mutations cause impaired protein translation in human RTT brain. We use a combination of in vitro and in vivo model systems, including murine and human neural stem cells (self-renewing and differentiated cells into neurons and astrocytes), along with a *MECP2*-deficient transgenic mice, and human post-mortem brain tissues. We show that in addition to disturbed epigenetic mechanisms in Rett Syndrome, major cell signalling pathways upstream of protein translation is impaired in the brain of Rett Syndrome patients and in vitro cellular models of Rett Syndrome. Our recent results provide exciting new insights on how molecular deficiencies at the cellular and molecular levels cause compromised brain function in Rett Syndrome, and other MeCP2-associated brain disorders such as autism.

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