Dendritic spines and Akt/mTor pathway defects in a mouse model of Rett syndrome

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Increasing evidences point to alteration in the formation and refinement of synaptic circuits as central causes of the pathological signs shown by individuals suffering from neurological disorders associated with intellectual disabilities. Rett syndrome (RTT) is a rare progressive disorder associated with severe mental retardation occurring mainly in girls during early childhood that is caused in the majority of cases by mutations in methyl-CpG-binding protein 2 (MeCP2). Although a relative large number of animal models for RTT has been available for several years, beside palliative care, no effective treatment is currently available for this disease. This absence mostly stems from our ignorance about the mechanisms leading from the genetic defect to the alterations occurring at cellular and neural system level. To study the effects of RTT on neuronal organization, we produced Mecp2-KO/Thy1-GFP mice expressing GFP only in selected neuronal populations of the forebrain. The analysis using confocal microscopy on fixed tissue revealed neuron-specific abnormalities of dendritic spines organization. In addition, using two-photon microscopy to image spines in-vivo through a cranial window we found that dendritic spines short-term motility was drastically reduced in presymptomatic KO animals compared to WT littermates. Next, we found that the synaptic defects associated with RTT may be caused by abnormal protein synthesis rates. Phosphorylation levels of rpS6, a component of the 40S ribosomal subunit, is severely altered in different neuronal subpopulations across the brain of presymptomatic MeCP2-KO mice and in symptomatic heterozygous female mutants. Moreover, severe defects of protein synthesis initiation were present the brain of presymptomatic Mecp2 mutants that were not restricted to specific subset of transcripts. Finally, we discovered a general dysfunction of the Akt/mTOR signaling associated with the disease progression. Our results indicate that defects in the AKT/mTOR pathway are responsible for the altered translational control in Mecp2 mutant neurons and disclosed a novel putative biomarker of the pathological process. Importantly, these data prompted us to test novel potential therapeutic interventions to restrain or ameliorate symptoms of RTT in mice. Finally, because MeCP2 mutation have been identified in individuals diagnosed with anxiety, learning disabilities, autism and Angelman-like syndrome, it is conceivable that future therapies will be clinically relevant not only to RTT but also to the disorders that are caused by MECP2 dysfunction.

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