rett syndrome research trust

Knowledge Gaps

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WHAT WE KNOW

- Mutations in MeCP2 give rise to Rett Syndrome and related disorders.
- MeCP2 is important for the proper function of specific cells, in particular neurons and glia.
- MeCP2 deficiency leads to neuronal circuit abnormalities.
- MeCP2 is a nuclear protein that binds to methylated DNA throughout the genome.
- Restoration of MeCP2 expression in the whole brain or specific cell types reverses overt phenotypic features in the mouse model.

UNANSWERED QUESTIONS IN THE FIELD

- How is expression of MeCP2 regulated in the brain?
- Does MeCP2 have a role in transcriptional regulation that would perhaps be difficult to see using conventional microarray technologies?
- Does MeCP2 play a direct role in regulating gene expression?
- Does MeCP2 play a histone-like role in regulating the structural integrity of the genome? Should the function of MeCP2 be examined on a genome-wide scale rather than in a locus-specific manner?
- Do other proteins compensate for MeCP2? For example does the up-regulation of histone H1 in the MeCP2 knock-out brain suggest that MeCP2 and histone H1 serve similar functions within the nucleus? Would these types of compensatory changes be relevant with MeCP2 mutations that do not eliminate MeCP2 expression?
- Do particular RTT mutations modulate the molecular function of MeCP2?
- Is mutated MeCP2 unstable? If so, can stabilizing drugs be beneficial?
- Is mutated MeCP2 detrimental or merely hypofunctional?
- Why is overexpression of MeCP2 toxic?
- What are the roles of the MeCP2 isoform(s)?
- How complete is the rescue of complex brain functions (cognition and network wiring) upon restoration of MeCP2 expression?
- What role does MeCP2 play in dendrite and synapse development and how does its dysfunction contribute to the Rett phenotype?
- Are neural circuits in Rett syndrome patients in fact largely intact?
- Which deficits in neuronal function are cell-autonomous, which depend on complex network interactions?
- In females what proportions of cells need to be wild–type to have a “normal” phenotype?
- Does CNS knockout of MeCP2 recapitulate all the symptoms of RTT? Also, would knockout of MeCP2 in extra-neuronal tissues lead to RTT-like consequences?
- Do other proteins serve the ‘MeCP2 function’ in extra-CNS cell types? For example, is MeCP2 the neuronal histone H1?
- Is MeCP2 modified in response to extracellular stimuli in cells outside the nervous system? Are neuronal activity-dependent modifications of MeCP2 part of what makes its role in the neuron so crucial to CNS development?
- What is the role of the immune system in RTT pathogenesis?
- Do human modifier genes impact the severity of the disease?