Can non-invasive interventions synergistically enhance the efficacy of MECP2 gene therapy?

Sarah Sinnett, PhD
University of North Carolina at Chapel Hill
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RTT is a neurodevelopmental disorder caused by inactivating mutations in the transcription regulator methyl-CpG-binding protein 2 (MeCP2). Collaborative improvements in MECP2 gene transfer (i.e., dose, route, and vector design) have marked a recent milestone in pre-clinical RTT research. Specifically, intraCSF administration of an improved second-generation AAV/MECP2 vector can extend Mecp2-/y survival at a relatively low dose, without inducing weight loss, gross neurological side effects, or liver toxicity. In a clinical setting, however, a fully optimized MECP2 gene therapy may not be a "magic bullet" that instantly improves quality of life for patients. After gene transfer, patients will need continuous interventions, such as physical therapy or cognitive enrichment at school. In RTT mice, can non-invasive interventions enhance the therapeutic benefits of MECP2 gene transfer additively or synergistically? The ability of non-invasive interventions (e.g., exercise and environmental enrichment [EE]) to induce functional and molecular changes in the brain is well-established. For example, researchers have shown that exercise drives the phosphorylation of MeCP2 and the expression of brain-derived neurotrophic factor (BDNF), a MeCP2-dependent protein that modulates neuronal circuitry and can partially compensate for MeCP2 loss in mice. To our knowledge, however, no publications have determined if non-invasive approaches can help "fire and wire" neuronal circuits after MECP2 gene transfer. Interestingly, Kondo and colleagues have published data suggesting that MeCP2 genetic dosage and EE (which typically includes an exercise component) may regulate behavior interdependently in RTT mice. By identifying interactions between MECP2 gene transfer and EE or exercise in RTT mice, we may come closer to unleashing the full potential of MECP2 gene transfer. Furthermore, a head-to-head comparison of invasive and non-invasive interventions will ultimately provide clinicians and parents with a well-rounded risk/benefit assessment of different RTT interventions or combinations thereof. As state-of-the-art genetic approaches evolve (e.g. viral vectors, nanotechnology, or gene editing), insights from this study will continue to benefit patients. In the meantime, synergistic effects upon motor or emotional phenotypes will direct scientists toward identifying brain region-specific, disease-relevant plasticity-regulating proteins that may be targeted by combinatorial treatments.