MISREGULATION OF GROWTH-DIFFERENTIATION FACTOR 11 (GDF11) IN MECP2-RELATED DISORDERS

Sameer S Bajikar[1], Huda Y Zoghbi[2]

[1] Baylor College of Medicine, Department of Molecular & Human Genetics

[2] Baylor College of Medicine, Molecular & Human Genetics, N/A

Background: Loss-of-function mutations or duplication in methyl-CpG binding protein 2 (MECP2) cause two severe neurodevelopmental disorders: Rett syndrome and MECP2-duplication syndrome, respectively. While the genetic cause of these disorders is known, the mechanism by which disruption in MeCP2 levels leads to pathogenesis unknown. Disruption in normal levels of MeCP2 causes a mild change in expression of thousands of genes. The objective of this study is to identify robustly misregulated transcripts in mouse models of MeCP2-disorders to reveal candidate mediators of pathogenesis.

Materials/Methods: I collated RNA-sequencing data sets generated in Mecp2-null mouse brains. These profiles were collected across different brain regions and different studies. I normalized the profiles to wild-type controls and pooled the replicates. Using nonparametric statistics, I identified the most robust transcriptional changes in Mecp2-null mouse models.

Results: I identified roughly 100 genes that were robustly misrelated, and identified Growth differentiation factor 11 (Gdf11) as a gene sensitive to MeCP2-levels. Gdf11 is downregulated in Mecp2-null models, while upregulated in MECP2-transgenic models. Additionally, Gdf11 expression levels are returned to wild-type levels when MeCP2 levels are normalized. The opposing regulation of Gdf11 by MeCP2 implicates GDF11 misregulation as one potential driver of some phenotypes in Rett and MECP2 duplication syndromes. GDF11 is a transforming growth factor beta family ligand that is a critical patterning morphogen for the skeletal system. However, despite broad expression throughout the brain, the role of GDF11 in brain development and homeostasis is unknown

Conclusions: On going and future work will test if modulating GDF11 levels specifically in the brain using either will on its own cause aberrant neurological phenotypes. Next, I will test if normalization of GDF11 levels rescues neurological phenotypes seen in mouse models of MECP2 disorders. In sum, I have found that GDF11 is misregulated in MECP2-related disorders, and I will test its potential as a therapeutic modifier of these disorders.