

Developmental Pediatrics

Title: IMPLICATION OF BIVALENT CHROMATIN AND MICRORNA AS POTENTIAL FOLIC ACID RESPONSIVE TARGETS (FART) IN FOLATE MEDIATED RESCUE OF NEURAL TUBE DEFECTS IN MOUSE MODEL OF SPINA BIFIDA

Presenting Author: C Shekhar Mayanil, Neural Tube Research Laboratory, Department of Pediatric Neurosurgery, Developmental Biology Program, Children's Memorial Research Center and Northwestern University Feinberg School of Medicine

Additional Authors:

- Shunsuke Ichi, Neural Tube Research Laboratory, Department of Pediatric Neurosurgery, Developmental Biology Program, Children's Memorial Research Center and Northwestern University Feinberg School of Medicine
- Hiromichi Nakazaki, Department of Neurosurgery, Jikei University School of Medicine, Tokyo, Japan
- Fabricio Costa, Epigenomics and Cancer Biology Program, Children's Memorial Research Center, Department of Pediatrics, Northwestern University Feinberg School of Medicine
- Yueh-Wei Shen, Neural Tube Research Laboratory, Department of Pediatric Neurosurgery, Developmental Biology Program, Children's Memorial Research Center and Northwestern University Feinberg School of Medicine
- Tadanori Tomita, Neural Tube Research Laboratory, Department of Pediatric Neurosurgery, Developmental Biology Program, Children's Memorial Research Center and Northwestern University Feinberg School of Medicine
- David McLone, Children's Memorial Hospital, Medical Director of Spina Bifida Program, Professor of Pediatric Neurosurgery Northwestern University Feinberg School of Medicine

Background: Spina Bifida is one of the most common birth defects, but the mechanisms underlying this disorder remain largely unknown. Spina Bifida is preventable in 60% of cases, by maternal folic acid (FA) supplementation prior to conception suggesting that there is an epigenetic component to this developmental abnormality. To date there are no epigenetic markers available for predicting whether this birth defect is folate responsive or folate non-responsive. The purpose of this study is to discover novel epigenetic markers for effective diagnosis of folate responsive and non-responsive spina bifida and identify potential therapeutic targets to treat this defect in utero.

Method: We used caudal neural tubes from E10.5 wild type and Sp^{-/-} (Spotch) embryos for explant cultures on Matrigel®. Upon differentiation, the migrated neural crest cells were immuno-stained for methylated histone H3 antibodies. Acid extracted histone preparations from caudal neural tube of wild type, Sp^{-/-} and Sp^{-/-} (FA-rescued) embryos were immunoblotted using methylated histone H3 antibodies. TaqMan MicroRNA (miRNA) assays (Reverse Transcription Kit from Applied Biosystems) were used to quantify the levels of ~384 mature miRNAs. Expression of ~365 miRNAs was characterized in purified total RNA from caudal neural tubes of wild type, Sp^{-/-}, and Sp^{-/-} (FA-rescued) embryos.

Results: (i) Di-methylation of histone H3K4 and H3K27 is increased in Sp^{-/-} (NTD) embryos; (ii) Folate reverses the di-methylation of H3K4 and H3K27 in Sp^{-/-} (FA rescued) embryos; (iii) Folate targets the miR-129-3p, miR-138, miR-344, miR-377 among others that regulate JMJD3, a H3K27 demethylases.

Conclusion: Our studies using an animal model of Spina Bifida provide the first evidence that demethylation of histone H3K4 and H3K27 may play a very crucial role in the posterior neural tube closure and the molecular etiology of Spina Bifida. These epigenetic markers have potential for use as predictive tools as well as therapeutic targets in the treatment of Spina Bifida.