

Pediatric Neurosurgery Research at Children's Memorial Medical Center and Children's Memorial Research Center, Chicago

Lack of proper neural tube closure as in Spina bifida is the root cause of all the developmental abnormalities such as Hydrocephalus and Chiari II malformation. With open neural tube the cerebrospinal fluid leaks, resulting in the brain to descend into first cervical spine. Thus essentially all Spina Bifida patients have the intermediate form (Chiari Type II or Arnold-Chiari malformation). Many changes of the brain are associated with this abnormality such as Hydrocephalus. Thus proper closure of the neural tube during development is absolutely necessary if we want to eliminate Chiari malformation and Hydrocephalus from human population.

An estimated 3,000 pregnancies in the U.S. are annually affected by neural tube defects. Research shows that if all women who could become pregnant consumed recommend amounts of folic acid (FA) before and during pregnancy, the risks of neural tube defects such Spina Bifida could be decreased by 70%. FA may also prevent other birth defects, including cleft lip and palate and heart defects. ***These birth defects are diagnosed in the second trimester when it is too late for medical intervention. Currently, the mechanisms behind FA rescue of neural tube defects are not well understood. Identifying the mechanism and targets by which FA rescues these defects is expected to provide leads for future development of novel therapeutics that could potentially repair spina bifida and related birth defects in utero.***

In a study using an animal model (*Spotch* or *Sp^{-/-}*) that fails to show proper neural tube closure, resulting in Spina Bifida, a team led by Drs. David McLone, Tadanori Tomita and Chandra Shekhar Mayanil has shed light on how FA influences neural cell development. The group showed that FA rescued the proliferation potential of neural crest stem cells from *Sp^{-/-}* animals via epigenetic mechanisms. Epigenetics is the study of inherited changes in phenotype (appearance) or gene expression caused by mechanisms other than changes in the underlying DNA sequence. Epigenetic mechanisms are important links between environmental factors and gene expression. Since cell proliferation and differentiation are very active in the embryo or fetus, epigenetic changes can profoundly impact development.

Histone modifications are epigenetic changes that regulate diverse biological processes. This study focused on histone H3 (H3K27) methylation. The data suggest that changing H3K27 methylation is involved in the open neural tube phenotype in *Sp^{-/-}* embryos. Levels of H3K27 reverse back toward normal in *Sp^{-/-}* neural tube treated with FA.

To identify potential epigenetically altered genes, the group focused on two genes, *Hes1* and *Neurog2*, whose activity is altered in *Sp^{-/-}* embryos. *Hes1* is responsible for progenitor cell proliferation and maintenance of stem cell character, and *Neurog2* is critical for sensory neurogenesis. The study suggests that H3K27 is associated with *Hes1* promoter during early embryonic development and with *Neurog2* promoter during the onset of neurogenesis. These associations are gene and developmental time-dependent, indicating a dynamic interplay of fine-tuning stem cell proliferation and differentiation.

The research is published online in the September 10, 2010 issue of the *Journal of Biological Chemistry*. Senior author Mayanil is Assistant Professor of Neurological Surgery at Northwestern University Feinberg School of Medicine, Director of the Neural Tube Research Program and a member of the Developmental Biology Program of Children's Memorial Research Center. First author is Shunsuke Ichi, a member of the Mayanil laboratory and of the Department of Neurosurgery, University of Tokyo.