Solving the Puzzle of the "Silent Angels" – Modifying Rett Syndrome Gene Rescues Deficits

Dr. Eminy H.Y. Lee, Distinguished Research Fellow at the Institute of Biomedical Sciences, Academia Sinica recently discovered that modification of a gene known to often be mutated in the autism spectrum disorder "Rett Syndrome" and other neuro-developmental disorders, can rescue the behavioral deficits of social interaction, fear memory and synaptic deficit in mice. The research team found that a post-translational modification of the MeCP2 protein could rescue the behavioral and neural deficits in *Mecp2* conditional knockout mice. These results advance our understanding of Rett Syndrome and suggest new therapeutic strategies. The results were published in the February 4, 2016 issue of *Nature Communications*.

Rett Syndrome first became well known through a documentary film entitled "Silent Angels: The Rett Syndrome Story" narrated by actress Julia Roberts in 2000. It is a neuro-developmental disorder that is known to be closely linked to the gene *MECP2*. Rett Syndrome occurs in approximately 1:10,000 live female births; boys with this disorder normally do not survive. Children with Rett Syndrome usually develop normally before one and a half years old. After that, abnormal symptoms including deficits in motor function, social ability, learning and memory performance and emotional control occur that progress rapidly. Motor function deficit is often characterized by twisting hands, rubbing hands together or even placing hands into the mouth. Rett Syndrome cannot be cured. So far, drugs can only alleviate the symptoms.

The research team led by Dr. Lee recently found that the MeCP2 protein is modified by SUMO proteins – a process called SUMOylation. They found a consistent and significant decrease in MeCP2 SUMOylation in several *MECP2* mutations that are often identified in Rett Syndrome patients. Using *Mecp2* conditional knockout mice as a model, they found that increase in MeCP2 SUMOylation successfully rescues the behavioral and neural deficits in these mice. It also increases the level of *Bdnf* gene expression. BDNF protein has been demonstrated to play a very important role in enhancing learning and memory, neuroplasticity and even protection against neurodegenerative diseases.

In addition, the research team also found that insulin-like growth factor-1 (IGF-1) and corticotrophin-releasing factor (CRF) both significantly increase the level of MeCP2 SUMOylation in rat brain. Dr. Lee said, "Few reports have shown that IGF-1 has a therapeutic effect in Rett Syndrome patients. On the other hand, CRF has been demonstrated to facilitate learning and memory and increase *Bdnf* gene expression in the brain. Our research result can perhaps provide a novel direction for the therapeutic potential of corticosterone against Rett Syndrome in the future."

There are three co-first authors of this paper. Dr. Derek Tai graduated from the Graduate Institute of Life Sciences, National Defense Medical Center in Taiwan 6 years ago, and now works as a postdoctoral fellow at Harvard University; Mr. Y.C. Liu is a third-year Ph.D. student enrolled in the Graduate Institute of Life Sciences, National Defense Medical Center, and Dr. W.L. Hsu is currently a postdoctoral fellow in Dr. Lee's laboratory.

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The complete article is available at the *Nature Communications* journal website at: http://www.nature.com/ncomms/2016/160204/ncomms10552/abs/ncomms10552.html