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Tet1 overexpression leads to anxiety-like behavior and enhanced fear memories via the activation of calcium-dependent cascade through Egr1 expression in mice

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Ten-eleven translocation methylcytosine dioxygenase 1 (Tet1) initiates DNA demethylation by converting 5-methylcytosine (5-mC) to 5-hydroxymethylcytosine (5-hmC) at CpG-rich regions of genes, which plays a key role in adult neurogenesis and memory. In addition, the overexpression of Tet1 with 5-hmC alteration in patients with psychosis has also been reported, for instance in schizophrenia and bipolar disorders. The mechanism underlying Tet1 overexpression in the brain, however, is still elusive. In the present study, we found that Tet1-transgenic (Tet1-TG) mice displayed abnormal behaviors involving elevated anxiety and enhanced fear memories. We confirmed that Tet1 overexpression affected adult neurogenesis with oligodendrocyte differentiation in the hippocampal dentate gyrus of Tet1-TG mice. In addition, Tet1 overexpression induced the elevated expression of immediate early genes (IEGs), such as Egr1, c-fos, Arc, and Bdnf followed by the activation of intracellular calcium signals (i.e., CamKII, ERK, and CREB) in prefrontal and hippocampal neurons. The expression of gamma-aminobutyric acid (GABA) receptor subunits (Gabra2 and Gabra4) fluctuated in the prefrontal cortex (PFC) and hippocampus. We evaluated the effects of Tet1 overexpression on intracellular calcium-dependent cascades by activating the Egr1 promoter *in vitro*. Tet1 enhanced Egr1 expression, which may have led to alterations in Gabra2 and Gabra4 expression in neurons. Taken together, we suggest that the Tet1 overexpression in our Tet1-TG mice can be applied as an effective model to study various stress-related diseases that show hyperactivation of intracellular calcium-dependent cascades in the brain.

Speaker Biography

Wookbong Kwon is currently studying for PhD at Kyungpook National University in Korea. His current laboratory is focusing on elucidating gene function and their relation to diseases using various transgenic mice models.

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