OMICS Group Conferences
Accelerating Scientific Discovery

International Conference and Exhibition on
Neurology & Therapeutics

May 14-16, 2012 Embassy Suites Las Vegas, USA

Small GTP-binding proteins as a therapeutic target for cognitive deficiencies

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During the process of learning and memory, neuronal synapses undergo changes referred to as synaptic plasticity, which has been reported to be abnormal in several autistic disorders such as Fragile X syndrome. Rac1, a protein of the Rho subfamily of GTP binding proteins, is largely known for its involvement in cytoskeleton remodeling, and has been implicated in neuronal development. However, the functional role of Rac1 in adult neuronal signaling is relatively unknown. We have previously demonstrated that Rac1 is highly expressed in the adult mouse hippocampus, a part of the brain crucial for learning and memory. In vitro studies in hippocampal slices indicated that activation of the hippocampal NMDA receptor results in membrane translocation and activation of Rac1. Likewise, in vivo studies revealed that activation of Rac1 is associated with fear learning in the adult mice. Moreover, we have recently reported that regulation of Rac1 is altered in a mouse model of Fragile X syndrome. However, whether the aberrant dendritic spine morphology and altered long-term plasticity observed in this autistic syndrome is related to Rac1 upregulation remains unclear.

Thus, to evaluate the importance of Rac1 in plasticity and learning we have generated a mouse bearing a conditional inactivation of the rac1 gene in the hippocampus. In these mice, we observed that loss of Rac1 leads to a significant reduction in spine density, impaired LTP and LTD as well as deficient learning and memory capabilities. Collectively, these data suggest that Rac1 is an important protein required for proper dendritic spine morphogenesis, long-term synaptic plasticity, and learning and memory. Since these phenomena are abnormal in some diseases bearing cognitive impairment and autistic traits, Rac1 might represent an interesting target in the study of possible therapies for these diseases.

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