2021 Fall
LIFE SCIENCES SEMINAR

"Dysfunction of NMDA receptors implicated in neuronal model of autism spectrum disorder"

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- **Inquiry: Prof. Joung-Hun Kim(279-2347)**
- **Abstract:**

Autism is a disorder of neural development, characterized by two types of symptom such as communication and social deficits and repetitive behaviors. Autism spectrum disorder or ASD describes a broad range of conditions including autism, Asperger syndrome, and mild forms of autism. There are many factors causing ASD. Genetic factors, however, seem to play more dominant roles in ASD pathogenesis than any other common psychiatric disorders. We have used Shank2 KO mice as a genetic model of ASD and showed that deletion of Shank2 gene in mice, which is identical to the SHANK2 mutation found in human autism patient, showed a reduction in the NMDA receptor function and impaired social interaction in these mice. In a different set of experiment, we generated telencephalic induced neuronal (iN) cells from iPSCs derived from an ASD patient with a heterozygous point mutation in the DSCAM gene. The expression level of DSCAM in dendrites were significantly decreased in ASD compared to control iN cells. RNA sequencing analysis revealed that several synaptic function-related genes including NMDA receptor subunits were downregulated in ASD iN cells. Furthermore, DSCAM was co-localized with NMDA-R components in the dendritic spines of iN cells whereas their co-localizations were significantly reduced in ASD iN cells. To examine the effect of *Dscam* mutation on behavioral phenotypes *in vivo*, we generated a neural stem cell-specific Dscam heterozygous knockout mouse model. This mouse line showed deficits in social interaction and social memory with reduced NMDA-R currents, suggesting that DSCAM mutation causes pathological symptoms of ASD by dysregulating NMDA-R function. In summary, by using human ASD patient-derived iN cells and mutant mouse models, we revealed a novel ASD pathophysiology in that certain mutations may lead to autistic phenotypes by impairing NMDA-R function.