論 文 の 内 容 の 要 旨

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論　文　題　目

IQSEC2 Deficiency Results in Abnormal Social Behaviors Relevant to Autism by Affecting Functions of Neural Circuits in the Medial Prefrontal Cortex.

（論文の内容の要旨）

(Background and Aims) Lately, genes located on the sex chromosome have been associated immensely to the etiologies of a wide variety of developmental psychiatric disorders. Aberrant crosstalk at the level of synapse is presumably the major culprit underlying the pathophysiology of such neurological conditions manifested collectively in learning, memory, and behavioral abilities. One such potential candidate, the gene encoding IQ Motif and Sec7 Domain 2 (IQSEC2), located on the X-chromosome, has been linked to neurodevelopmental disorders, like intellectual disability, epilepsy, and certain forms of autism spectrum disorders (ASDs). We seek to elucidate the role of this molecule in physiology at the level of synaptic crosstalk, in relevance to ASDs.

(Materials and Methods) We used a global and local approach to justify our hypothesis by generating the CRISPR/Cas9-mediated knockout (KO) mouse model and shRNA mediated knockdown (KD) of IQSEC2 respectively. Major methodologies include patch-clamp recording from acute brain slices for quantifying the synapse physiology; in-utero electroporation for selective knockdown of IQSEC2 in pyramidal neurons; and stereotactic viral injection for expressing IQSEC2 isoform1 in the medial prefrontal cortex (mPFC) of mouse brain.

(Results) We have shown the involvement of this post synaptic molecule in relevance to the phenotypic manifestation of autism, more specifically the social behavioral aspect. Up-regulation of c-Fos expression in the mPFC by social stimulation was attenuated in IQSEC2 KO mice, implicating the significance of this brain region in IQSEC2 associated phenotypes. The AMPAR, NMDAR, and GABAR-mediated synaptic transmissions were also found to be impaired in the pyramidal neurons of mPFCs in IQSEC2 KO mice, with a more robust deficit in AMPAR mediated synaptic transmission. The KD approach recapitulated the synaptic impairments, attributing the synaptic deficits to the postsynaptic deletion of IQSEC2. Most importantly, the social behavioral deficits and synaptic impairments were successfully abolished when we reconstituted the longest isoform of IQSEC2 to the mPFC, of the KO mice by an adeno-associated viruses (AAV)-mediated gene delivery system.

(Conclusion) We generated IQSEC2 KO mice and studied their behavior and electrophysiological properties focusing on the mPFC. The IQSEC2 KO mice exhibited overgrooming and social deficits reminiscent of the symptoms of autism. AMPAR, NMDAR, and GABAR-mediated synaptic transmissions were impaired in pyramidal neurons in layer 5 of the mPFC in IQSEC2 KO mice. Re-expression of IQSEC2 in the mPFC rescued both synaptic and social behavioral phenotypes, suggesting that an impairment in the neural function in the mPFC may be responsible for social deficits in IQSEC2 KO mice.