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Shinichi Hirose

Fukuoka University, Japan

Application of induced pluripotent stem (iPS) cells in intractable childhood disorders

While induced pluripotent stem cells (iPSCs) are generally considered to be used in regenerative medicine, they can also be used to reproduce disease pathophysiology *in vitro*. This ability to replicate disease pathophysiology using iPSCs may be beneficial for intractable childhood disorders, specifically those involving the central nervous system, such as Dravet Syndrome. Dravet Syndrome, one of the intractable genetic epilepsies affecting children, is caused by mutations of *SCN1A*, the gene encoding the α1 subunit of Na+ channels in the brain. To understand the pathomechanisms of Dravet Syndrome, we established iPSC lines from a patient harboring a pathological *SCN1A* mutation and differentiated the iPSCs into neuronal cells. We found, for the first time in humans, that the derived inhibitory GABAergic neurons had impaired action potentials compared to neurons derived from control iPSC lines. This finding is consistent with results from genetically engineered murine models with *Scn1a* mutations. Thus, the pathomechanisms of Dravet Syndrome can be attributed to dysfunction of the inhibitory interneurons, termed interneuronopathy, due to *SCN1A* mutations. The discovery of these molecular pathomechanisms aligns with clinical observations that some anti-epileptic drugs that block Na+ channels precipitate seizures in patients with Dravet Syndrome. This new understanding of the pathomechanisms of Dravet Syndrome should open fresh avenues for novel drug development. Additionally, current technologies are able to readily introduce any mutation into iPSCs, which can facilitate high-throughput iPSC screening platforms for new potential drugs that target affected organs, even in rare genetic intractable childhood disorders.

Biography

Shinichi Hirose, MD, PhD is a Professor of Pediatrics, Head of both the Department of Pediatrics and the Research Center for Molecular Pathomechanisms of Epilepsy at Fukuoka University, and a member of the standing committee of the International Pediatric Association (IPA). His interests are in the molecular genetics of epilepsies. He has worked extensively on causative mutations and their molecular consequences in the neuroscience mechanisms underlying epilepsies, and has published extensively on the molecular pathomechanisms of epilepsies. He is the principal investigator on numerous clinical studies and has studied many childhood diseases including epilepsies, metabolic diseases, and inherited diseases

Email: hirose@fukuoka-u.ac

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