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Recapitulating malformations of cortical development via induced pluripotent stem cell technology

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Background: Progress in our understanding of somatic cell reprogramming, particularly the isolation and characterization of human induced pluripotent stem cells (iPSCs) opened new avenues for modeling human disease. iPSCs allow the generation of large numbers of genetically modifiable cells specific to the underlying human genetic background, and form an unparalleled opportunity to gain new insight into disease pathophysiology. This will further lay the foundation for the development of patient specific pharmacological assays and/or stem cell based therapies. We focused on Walker Warburg Syndrome (WWS), a rare and severe form of lissencephaly paired with congenital muscular dystrophy. Most children die before the age of three years. Several genes have been implicated in the etiology of this syndrome, however, to this date the pathogenesis is poorly understood. In addition, none of the animal models appears to faithfully reflect the human condition. Patient derived iPSCs, however, allow the targeted differentiation of cells into tissue specific phenotypes of brain and muscle, and thus, provide an assay for the recapitulation of disease specific pathophysiology.

Design: iPSCs lines were derived from skin biopsy specimens of patients with WWS and normal age matched controls. The generation of iPSCs followed established protocols using nucleofection (Amaza system) of episomal plasmids expressing OCT3/4, SHp53, SOX2, KLF4, LIN28, and MYC. The cells were grown in culture and differentiated into all lineages of the human brain. Furthermore, since one of the hallmark features of lissencephaly is altered neuronal activity, this system forms a unique opportunity to monitor electrical activity of iPSC derived neurons.

Result: Directed differentiation of iPSCs into neuronal precursors was demonstrated *in vitro* with antibodies for CNS phenotypes, like GFAP, TUJ1, Tbr1/2. Furthermore, neuronal activity was monitored with ultrasensitive fluorescent protein calcium sensors (GCaMP6) and showed altered neuronal activity in neurons derived from patients versus normal controls.

Conclusion: This model allows the phenotypic recapitulation of complex neurogenetic traits, and provides insights into the pathophysiology of human forms of malformations of cortical development. The combination of technologies offers a unique opportunity to model human neurological disease and hold promise for the development of new treatment strategies.

Biography

Anita Huttner started her career as MD at University of Erlangen-Nurnberg, Germany in 1998. She worked as Clinical Fellow at Yale Medical School-Yale-New Haven Hospital & Harvard Medical School-Brigham and Women's Hospital and Children's Hospital. She has completed her Pre-/Post-doctoral fellow at National Institutes of Health. Currently, she is working as an Associate Professor of Pathology at Yale University School of Medicine.

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