Institute of Human Genetics

Division of Stem Cell Biology

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Research focus
- Stem cell modeling of Parkinson's disease
- Stem cell models of motor neuron disease
- Genetic pain disorders
- CRISPR/Cas9 gene editing of human pluripotent stem cells

Structure of the Division

Professorship: 1
Personnel:
- Doctor (of Medicine): 1
- Scientists: 2 (thereof funded externally: 1)
- Graduate students: 12

Clinical focus area
Speaker of the Center for Rare Diseases (ZSEER)

Research

Research at the Division of Stem Cell Biology focuses on modeling CNS diseases using genome editing and human stem cell-based models.
The physiological and pathological functions of the human brain are puzzling. Post-mortem tissue allows a structural analysis of the brain. In order to better understand the development and function of the brain, dynamic and/or functional investigations between different human brain cells are necessary. The generation of brain cells from human pluripotent stem cells in multidimensional cultures gives novel insights into structural and dynamic interactions. Specifically, we investigate neurodegeneration and regeneration in neurodegenerative and other neurologic diseases.

Stem cell modeling of Parkinson's disease

PI: Dr. I. Prots, Prof. Dr. B. Winner
Parkinson s disease (PD) is a progressive neurodegenerative disorder characterized by the loss of midbrain neurons. The accumulation of alpha-synuclein (αSyn) and inflammation are suggested to play a crucial role for neurodegeneration in PD. We investigate the mechanisms of their contribution to neuronal loss and their possible interplay during PD pathology.
To model PD pathology in human system, we differentiate neurons from patient-derived induced pluripotent stem cells (iPSC) in collaboration with the Division of Molecular Neurology. We demonstrated that the formation of small oligomeric αSyn aggregates reduces mitochondrial axonal transport and impairs axonal and synaptic integrity in human neurons, including PD patient iPSC-derived neurons. Axonal transport defects could be rescued by using a compound inhibiting αSyn oligomer formation.
To uncover neuroinflammatory pathways in human PD pathology, we developed a human autologous co-culture of peripheral T cells and iPSC-derived midbrain neurons from PD patients and controls. We showed that T cells induce cell death of midbrain neurons in sporadic PD by IL-17, upregulation of IL-17 receptor, and NFκB activation. In the blood of PD patients, higher frequencies of IL-17-producing T cells were evident and increased numbers of T cells were detected in postmortem PD midbrain tissues. Blockage of IL-17 or IL-17R rescued the neuronal death. Possible involvement of IL-17-producing T cells in PD might revise our understanding of how PD neurodegeneration can be promoted by systemic inflammation. Since inflammation can affect axonal transport, a challenging possibility of αSyn oligomer-induced axonopathy as underlying mechanism of Th17-induced neuronal death in human PD pathology will be further investigated.

Stem cell models of motor neuron disease

PI: Dr. M. Regensburger, Prof. Dr. B. Winner
Motor neuron diseases are characterized by the degeneration of the upper and/or lower motor neurons. Using different paradigms, embryonic stem cell lines or patient-derived iPSC are differentiated into upper and lower motor neurons. This enables us to analyze gene expression, proteins, neuronal integrity, formation of networks, and electrophysiological firing properties. In the most frequent type of hereditary spastic paraplegia (HSP), caused by mutations in the gene SPG4, we investigate alterations of the endoplasmic reticulum which cause length dependent upper motor neuron degeneration. Mutations in SPG11 are the most frequent cause of autosomal-recessive complicated HSP, which is characterized by multisystem neuronal degeneration. We analyze the effect of SPG11 mutations in different neuronal models including 3-dimensional brain organoids. We showed that GSK3 is hyperactivated in SPG11 and we are trying to reverse these specific signaling pathway abnormalities by therapeutic compounds and to establish patient-specific phenotype analyses. In neurons, differentiated from sporadic amyotrophic lateral sclerosis patients' cells, we identify disease-specific transcriptional signatures, which may cause individual susceptibility for motor neuron degeneration.
Thus, our overall goal is to better understand disease mechanisms in motor neuron diseases and to identify therapeutic targets for future translation into the clinic.

Genetic pain disorders

PI: Dr. E. Eberhardt
Chronic pain is a common health problem for which therapy often remains unsatisfactory. In recent years, studies of rare monogenic pain disorders have led to the identification of candidate genes and helped our understanding of the pathophysiology of pain. Among these are variants in peripheral voltage-gated sodium channels (Navs) that cause inherited pain syndromes, like primary erythromelalgia (IEM) and small-fiber neuropathy (SFN). Since rodent models lack the patient's individual genetic background, we obtained fibroblasts from two patients with chronic pain due to Nav1.9 linked SFN. Using a fibroblast reprogramming approach, we generated human induced pluripotent stem cells (hiPSCs) which we differentiate into patient-derived pain sensing peripheral neurons (nociceptors).
These nociceptors from pain patients in the dish show signs of neuronal hyperexcitability in patch-clamp recordings. Moreover, when grown on multi electrode array (MEA) plates, a pathological firing behavior was observed, mimicking the patient's C-fibers assessed in microneurography recordings. In MEA recordings, the FDA approved antiepileptic drug lacosamide strongly reduced electrical activity of hiPSC-derived nociceptors of SFN patients as compared to age matched control groups. Based on this preclinical prediction, one patient started off-label treatment with lacosamide. Within five days, pain ratings on numeric rating scale (0 no pain, 10 worst imaginable pain) decreased from 7.5 to 1.5. Simultaneously, spontaneous activity of the patient's C-fibers objectively assessed in microneurography recordings was significantly diminished. In summary, our findings led to an individualized translational therapeutic approach based upon patient-derived sensory neurons.

CRISPR/Cas9 gene editing of human pluripotent stem cells

PI: Dr. S. Turan

Gene editing is becoming increasingly important to generate human specific disease models with human embryonic stem cells or corrected patient derived induced pluripotent stem cells. Meanwhile, inefficient and labor-intensive gene editing techniques, such as Zinc finger nucleases or TALENs, were replaced by the CRISPR/Cas9 technique, which allows efficient gene editing in stem cells. Hence, mastery of this method is critical to generate and study loss or gain of function stem cell models.

Our laboratory uses the CRISPR method to generate knockout or knockin models of several genes, which play a critical role in neurodevelopment and intellectual disability (SOX11, ARID1B, TCF4), motor neuron diseases (SPG4, SPG11), and PD (SNCA). We successfully generated haploinsufficiency models of intellectually disability genes of SOX11 or ARID1B.

For proteins, where antibodies are not specific enough, we are currently in the process to use CRISPR to create endogenously FLAG or fluorescent reporter tagged reporter lines to validate novel protein-protein or protein-DNA interactions.

Teaching

The Division of Stem Cell Biology is involved in curricular teaching activities in Medicine and in the B.Sc. and M.Sc. degree programs Molecular Medicine as well as Cellular and Molecular Biology (M.Sc.), respectively.

Bachelor's and Master's theses as well as MD and PhD theses were supervised.

Selected publications

Sommer A, Maxreiter F, Krach F, Fadler T, Grosch J, Maroni M, Graef D, Eberhardt E, Riemenschneider MJ, Yeo GW, Kohl Z, Xiang W, Gage FH, Winkler J, Prots I, Winner B. Th17 Lymphocytes Induce Neuronal Cell Death in a Human iPSC-Based Model of Parkinson's Disease. Cell Stem Cell; 2018, 23(1):123-131

Prots I, Grosch J, Brazdis RM, Simmnacher K, Veber V, Havlicek S, Hannappel C, Krach F, Krumbiegel M, Schutz O, Reis A, Wrasidlo W, Galasko DR, Groemer TW, Masliah E, Schlotzer-Schrehardt U, Xiang W, Winkler J, Winner B. Alpha-Synuclein oligomers induce early axonal dysfunction in human iPSC-based models of synucleinopathies. PNAS; 2018, 115:7813-7818

Krach F, Batra R, Wheeler EC, Vu AQ, Wang R, Hutt K, Rabin SJ, Baughn MW, Libby RT, Diaz-Garcia S, Stauffer J, Pirie E, Saberi S, Rodriguez M, Madrigal AA, Kohl Z, Winner B, Yeo GW, Ravits J. Transcriptome-pathology correlation identifies interplay between TDP-43 and the expression of its kinase CK1E in sporadic ALS. Acta neuropathologica; 2018, 136(3):405-423

Pérez-Brangulí F, Buchsbaum IY, Pozner T, Regensburger M, Fan W, Schray A, Börstler T, Mishra H, Gräf D, Kohl Z, Winkler J, Berninger B, Cappello S, Winner B. Human SPG11 cerebral organoids reveal cortical neurogenesis impairment. Hum Mol Genet. 2018 Nov 22. doi: 10.1093/hmg/ddy397

Popp B, Krumbiegel M, Grosch J, Sommer A, Uebe S, Kohl Z, Plötz S, Farrell M, Trautmann U, Kraus C, Ekici AB, Asadollahi R, Regensburger M, Günther K, Rauch A, Edenhofer F, Winkler J, Winner B, Reis A. Need for high-resolution Genetic Analysis in iPSC: Results and Lessons from the ForIPS Consortium. Sci Rep. 2018 Nov 21;8(1):17201

Regensburger M, Prots I, Reimer D, Brachs S, Loskarn S, Lie DC, Mielenz D, Winner B. Impact of Swiprosin-1/Efhd2 on adult hippocampal neurogenesis. Stem cell reports; 2018, 10:347-355

International cooperations

Prof. F. H. Gage, Salk Institute for Biological Studies, La Jolla: USA

Prof. E. Jorum, Oslo University Hospital: Norway

Prof. E. Masliah, National Institute of Aging, Bethesda: USA

Prof. E. Reid, Cambridge Institute for Medical Research: UK

Prof. G. Yeo, University of California San Diego: USA