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
- CRISPR/Cas9 gene editing of human pluripotent stem cells

Structure of the Division

Professorship: 1
Personnel:
- Doctor: 4
- Scientists: 3
  (thereof funded externally: 2)
- Graduate students: 12

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

Research

The research of the Department of Stem cell biology focuses on modeling CNS disorders using genome editing and human stem cell technology. The physiological and pathological function of the human brain is still unsolved. Post mortem analyses are available for a structural investigation. In order to better understand brain development and degeneration, it is important to study the interaction of human brain cells. The generation of brain cells from human stem cells in multidimensional cultures enables novel relationships in structural and complex interactions. Our research focuses on neurodegeneration and regeneration in neurodegenerative and other neurological diseases.

Parkinson's disease Stem Cell Modeling
PI: PD. Dr. I. Prots, Prof. Dr. B. Winner
Parkinson's disease (PD) is a progressive, neurodegenerative disease characterized by the loss of midbrain neurons. It is believed that both alpha-synuclein (aSyn) accumulation and inflammation can play critical roles in neurodegeneration in PD. We investigate how this can lead to neuronal loss. We also investigate the interaction of neurodegeneration and neuroinflammation for PD pathology. To model PD pathology in a human model, we differentiate neurons from induced pluripotent stem cells (iPSC) from patients in cooperation with the molecular neurology department. We were able to show that the formation of smaller oligomer aSyn aggregates reduces axonal mitochondrial transport and compromises axonal and synaptic integrity in human neurons, including iPSC-derived neurons from PD patients. Axonal transport defects could be improved by using a substance that inhibits the formation of aSyn oligomers. To uncover the role of neuroinflammation in human PD pathology, we developed a human autologous co-culture from peripheral T-cells and iPSC-derived midbrain neurons from PD patients and controls. We were able to show that T cells induce the cell death of midbrain neurons in sporadic PD through IL-17 dependent signaling pathways, upregulate the IL-17 receptor and activate the activation of NF von B. More IL-17-producing T-cells were seen in the blood of PD patients, and an increased number of T cells was detected in post-mortem PD midbrain tissues. Blocking IL-17 or IL-17R decreased neuronal cell death in cell culture. A possible involvement of IL-17-producing T-cells in PD could reverse our understanding of how PD neurodegeneration can be promoted by systemic inflammation. We are currently investigating the influence of neuroinflammation on axonal transport in synucleinopathies.

Stem Cell Models of Hereditary Spastic Paraplegia (HSP)
PI: Dr. M. Regensburger, Prof. Dr. B. Winner
The group of HSPs comprises a heterogeneous symptom complex with the common characteristic of degeneration of the upper motor neuron. Using different paradigms, pluipotent stem cells are differentiated into different motor neurons. We compare patient cells with controls. This enables the analysis of gene expression, proteins, neuronal integrity, network formation and electrophysiological properties in neurons generated by patients in the cell culture. In the most common form of hereditary spastic paraplegia (HSP), which is caused by mutations in the SPG4 gene, we are investigating changes in the functional interaction between the endoplasmic reticulum and the cytoskeleton. Mutations in SPG11 are the most common cause of an autosomal recessive complex HSP, which is characterized by multisystem neuronal degeneration. We analyze the effect of SPG11 mutations in various neuronal models including three-dimensional cerebral organoids. Various affected cellular signaling pathways could be identified (lysosomal metabolism, mitochondrial function, GSK3), which are examined for potential therapeutic targets. Our overarching goal is to better understand the mechanisms of motor neuron disease and to identify therapeutic goals for future translation into the clinic.

Research into ALS using stem cell models
PI: Dr. F. Krach, Prof. Dr. B. Winner
Amyotrophic lateral sclerosis is characterized by the degeneration of the upper and lower motor neurons. At the molecular level, aberrant alternative splicing is believed to be the key mechanism of the disease. In order to shed light on these processes in more detail, we generate alpha motor neurons from iPSC from patients and controls and analyze the alternative splicing on a global level using RNA sequencing. To determine the cause of the splice changes, we integrate data sets on the RNA binding of various proteins that are known to influence alternative splicing. We want to use this knowledge to specifically identify RNA binding proteins, the modulation of which can represent a targeted target for future therapies.

CRISPR/Cas9 gene editing of human pluripotent stem cells
PI: Dr. S. Turan, Prof. Dr. B. Winner
Genome editing is becoming increasingly important in order to create human-specific disease models in human stem cell-based models. Inefficient and labor-intensive gene editing techniques such as zinc finger nucleases or TALENs have been replaced by the CRISPR / Cas9 technique, which enables efficient genome editing in stem cells. Therefore, this method is of crucial importance for examining models for neural developmental diseases and neurodegeneration. Our laboratory uses the CRISPR method to generate knockout or knockin models of multiple genes that play critical roles in nervous system development and cognitive impairment (SOX11, ARID1B, TCF4), motor neuron disease (SPG4, SPG11) and PD (SNCA). We succeeded in generating haploinsufficiency models for SOX11 or ARID1B. For proteins for which antibodies are not specific enough, we use CRISPR / Cas9 genome editing in order to create endo-genously marked reporter lines with FLAG or fluorescence reporter with the aim of generating new protein-protein or protein-DNA-Find interactions.

Teaching

The stem cell biology department participates with compulsory and elective subjects in the curriculum of medicine, cell and molecular biology and molecular medicine. Bachelor and master theses as well as medical and scientific doctorates are supervised.

Selected publications
Brazdis, R. M., Alecu, J. E., Marsch, D., Dahms, A., Simmnacher, K., Lorentz, S., . . . Prots, I. (2020). Demonstration of brain region-specific neuronal vulnerability in human iPSC-based model of familial Parkinson's disease. Hum Mol Genet, 29(7), 1180-1191. doi:10.1093/hmg/ddaa039
Perez-Branguli, F., Buchsbaum, I. Y., Pozner, T.,

Regensburger, M., Fan, W., Schray, A., . . . Winner, B. (2019). Human SPG11 cerebral organoids reveal cortical neurogenesis impairment. Hum Mol Genet, 28(6), 961-971. doi:10.1093/hmg/ddy397

Pozner, T., Regensburger, M., Engelhorn, T., Winkler, J., & Winner, B. (2020). Janus-faced spatacsin (SPG11): involvement in neurodevelopment and multisystem neurodegeneration. Brain, 143(8), 2369-2379. doi:10.1093/brain/awaa099

Simmnacher, K., Krach, F., Schneider, Y., Alecu, J. E., Mautner, L., Klein, P., . . . Winner, B. (2020). Unique signatures of stress-induced senescent human astrocytes. Exp Neurol, 334, 113466. doi:10.1016/j.expneurol.2020.113466

Sommer, A., Marxreiter, F., Krach, F., Fadler, T., Grosch, J., Maroni, M., . . . Winner, B. (2019). Th17 Lymphocytes Induce Neuronal Cell Death in a Human iPSC-Based Model of Parkinson's Disease. Cell Stem Cell, 24(6), 1006. doi:10.1016/j.stem.2019.04.019

International cooperations

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

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

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