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ABSTRACT BOOK

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Poster Presentations

T01 | Cell migration

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Disrupted-In-Schizophrenia 1 controls microglial movement and phagocytosis

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BACKGROUND: Microglia are the phagocytes of the central nervous system. They survey the micro-environment by migration during early development and by projecting and retracting protrusions at later stages. Appropriate control of microglial movement and phagocytosis is necessary to sculpt and maintain an efficient neuronal network. We study the neurodevelopmental gene Disrupted-In-Schizophrenia 1 (DISC1) as a regulator of microglial functioning. DISC1 disruption is associated with impaired neuronal networks and neurodevelopmental disorders. We hypothesize that loss of DISC1 in microglia impairs cytoskeletal control, disrupts their developmental functions, and contributes to neurodevelopmental disorders.

RESULTS: Our results show that DISC1 is highly expressed in mouse and human microglia. DISC1 locus impairment (LI) microglia phagocytose slower but their final synaptosome uptake is increased compared to wildtype (WT) microglia. DISC1 LI microglia migrate slower compared to WT microglia *in vitro* and in embryonic living brain slices. The relative idling time of *in vitro* and *ex vivo* DISC1 LI microglia is increased and the mean active migration speed is decreased. In contrast, we show that the surveyed brain area of DISC1 LI microglia in adolescent living brain slices is increased compared to WT microglia. Process extension towards laser-induced brain damage seems unchanged. The morphology, ramification index and cell size will be investigated and we are currently validating our findings using a DISC1 LI bone marrow transplantation in WT mice to exclude environmental effects of the DISC1 locus impairment on microglial behavior.

CONCLUSION: DISC1 is a molecular key controlling microglial movement during phagocytosis, migration, and branch motility.

T02-022C

Fast and efficient generation of oligodendrocytes from human induced pluripotent stem cells (hiPSCs)

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Background:
Oligodendrocytes (OLs) are highly specialized cells of the central nervous system (CNS) responsible for myelin production and metabolic support of neurons. Defects in OLs are crucial in several neurodegenerative diseases including multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS). Scarce access to primary samples and lack of efficient protocols to generate OLs from human pluripotent stem cells (hPSCs) are hampering our understanding of OL biology and the development of novel therapies.

Methods:
To promote the conversion of hPSCs into OLs, we have screened for a number of transcription factors (TFs) previously reported to be involved in OL generation. For this, hPSCs were fated for 8 days toward neural progenitors, and then transduced with an inducible lentiviral vector encoding for the different TFs.

Results:
We found that the overexpression of SOX10 was sufficient to generate O4+ oligodendrocyte precursor cells (OPCs) from hPSCs only 10 days after SOX10 induction. Generated OPCs expressed mature OL proteins as MBP or MOG. At the transcriptome level, generated OPCs resembled primary OPCs. To date, OPCs have been derived from eight different hPSC lines including those derived from patients with spontaneous and familial forms of MS and ALS, respectively. To test the functionality of generated OPCs, O4+ cells were co-cultured together with hPSC-derived neurons for additional 20 days, finding that O4+ cells were able to myelinate the neurons. Moreover, O4+ cells were injected intracerebrally in newborn shiverer RAG2$^{-/-}$ mice and the tissue was examined 16 weeks later, finding that generated OLs extended within the corpus callosum and generated functional myelin, demonstrating the functionality of generated cells also in vivo. The protocol also describes an alternative for viral transduction, by incorporating an inducible SOX10 in the safe harbor locus AAVS1, yielding ~100% pure OPCs. O4+ OPCs can be co-cultured with maturing hPSC-derived neurons in 96/384-well- format plates, allowing the screening of pro-myelinating compounds.

Conclusions:
We have developed a novel methodology for a fast (20 days from hPSC stage) and efficient generation of functional OLs, which allow testing of compounds involved in myelination. This technology will allow further studies to better understand human OL biology and the screening of potential compounds involved in myelination in a human setting.