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Abstract Booklet



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Oral Abstracts

Netherlands.

2. Department of Translational Neuroscience, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, the Netherlands.
3. Center for Biomix, Erasmus Medical Center, Wytemaweg 80, 3015 CN Rotterdam, the Netherlands.
4. Department of Neurology, Erasmus Medical Center, Rotterdam, the Netherlands.
5. Department of Clinical Genetics, VU Medical Center, Amsterdam, the Netherlands.
6. Department of Neuroimmunology, Netherlands Institute for Neuroscience, an institute of the Royal Netherlands Academy of Arts and Sciences, the Netherlands.
7. Department of Molecular and Cellular Neurobiology, CNCR, Amsterdam Neuroscience, VU University, Amsterdam, the Netherlands

Microglia are brain resident macrophages with phagocytic but also trophic functions. Mutations in several genes almost exclusively expressed in microglia cause severe white matter brain disorders by unknown mechanisms. Haploinsufficient mutations in colony-stimulating factor 1 receptor (CSF1R), cause adult onset leukoencephalopathy with axonal spheroids (ALSP), which often leads to death within 5 years after symptomatic onset. We generated an allelic series in zebrafish of *csf1ra* and *csf1rb* mutants to identify *csf1r*-dependent microglia changes. We showed that *csf1r* mutations lead to aberrant microglia density and distribution, and regional loss of microglia, whereas microglia were absent in homozygous mutants for both *csf1r* homologs. Previously, we identified the zebrafish microglia transcriptome, which shares high similarity with the human microglia transcriptome. In *csf1r* mutants with only 1 functional allele we found that remaining microglia still had a microglia-specific gene expression signature, indicating that they had normally differentiated. Strikingly, we also observed lower microglia numbers and widespread microglia depletion in post mortem brain tissue of ALSP patients. Either in zebrafish or in human disease, local microglia loss also presented in regions without obvious pathology. Together, this implies that CSF1R mainly regulates microglia density and that early loss of microglia could contribute to ALSP pathogenesis. In line with this, microglia depletion in the mouse leads to reduced cell numbers of the myelinating lineage, but is also being investigated as a potential therapy for neurodegenerative disease. Our results imply that microglia loss in humans could contribute to white matter disease and we will report on our progress in investigating the role of microglia in the brain's white matter.

O-57

Early life social isolation induced serotonergic deficits and their behavioural consequences in zebrafish (*Danio rerio*)

Zoltán Kristóf Varga^{1,2}, László Bíró¹, Diána Pejtsik¹, Áron Zsigmond³, Kornél Demeter³, Éva Mikics¹, Máté Varga^{3,4}, Manó Aliczki¹

1. Laboratory of Translational Behavioural Neuroscience, Department of Behavioural Neurobiology, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary
2. János Szentágothai Doctoral School of Neurosciences, Semmelweis University, Budapest, Hungary
3. Department of Genetics, Eötvös Loránd University, Budapest, Hungary
4. Semmelweis University "Lendület" Nephrogenetic Laboratory, Hungarian Academy of Sciences, Budapest, Hungary
5. Unit of Behavioural Studies, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary

Social isolation during sensitive periods e.g. post-weaning in rodents or childhood in humans, exerts devastating psychoneurological effects. Constructing animal models by isolating individuals of social species can be an effective tool to unravel the background of such phenomenon, however,

the validity of these are highly depends on the period of deprivation. Despite the many advantages of zebrafish, best to our knowledge there is no model based on the isolation of these social animals in a well-defined critical developmental period. Here we present a novel zebrafish model to study the physiological and behavioural effects of early life social isolation. We characterized an extensive behavioural metamorphosis during the first month of development, including the maturation of anxiety-like and social behaviour, coinciding with a highly sensitive and critical time-window. Chronic social isolation applied in this period decreased basal and increased challenge-induced whole-brain serotonin content and disrupted both novelty-induced and social anxiety in juvenile zebrafish. Immunohistochemical analysis confirmed that such changes in serotonin responses specifically targeting the dorsal pallidum indicating the engagement of limbic structures in behavioural impairment. Furthermore, we showed that acute treatment with clinical anxiolytic, partial 5HT1A receptor agonist buspirone, prevented social isolation-induced enhanced serotonin responses and associated behavioural changes, in a dose ineffective in socially reared fish. Taken together, we found that social isolation in a critical period reversibly disrupts juvenile phenotype of zebrafish, highlighting changes in the serotonergic system, in a similar extent and manner that of reported in higher vertebrates. These results suggest that the zebrafish model is suitable to explore the background mechanisms and design novel therapeutic interventions of social deprivation associated mental disorders.

O-58

Epigenetic control of Hematopoietic Stem Cell Development

Feng Liu¹

1. Institute of Zoology, Chinese Academy of Sciences

Hematopoietic stem cells (HSCs) are a population of multipotent cells that can self-renew and differentiate into all blood lineages. HSC development must be tightly controlled, which involves a complex of extrinsic signaling and intrinsic factors. Using the zebrafish and mouse models to study regulation of HSCs in vivo has greatly facilitated our understanding of HSC biology in vertebrates. I will talk about our recent progress on HSC development, with particular focus on how epigenetic factors control hemogenic endothelium-derived HSC specification through fine tuning of Notch signalling. These new findings may help to design new strategies into in vitro directed differentiation of HSCs.

O-59

Zebrafish *hai1* mutant embryos as an in vivo model to elucidate the dual face of the type II transmembrane serine protease Matriptase during carcinogenesis

Joy Armistead¹, Matthias Hammerschmidt²

1. Institute of Zoology – Developmental Biology,
2. University of Cologne, Germany

The type II transmembrane serine protease Matriptase 1 is up-regulated and its inhibitor *Hai1* down-regulated in multiple human carcinomas. Zebrafish *hai1a* mutants display compromised epithelial integrity and hyperplasia in the embryonic epidermis, coupled with moderate fragmentation of the cutaneous basement membrane. Strikingly, however, most mutant individuals heal spontaneously during later stages. We identified an EGFR – phospholipase D (PLD) – mTORC1 pathway downstream of Matriptase mediating its effects on basal keratinocytes. Chemical blockage of this pathway leads to a transient improvement, but a long-term worsening of the defects with more persistent carcinogenesis, pointing to a double-face of Matriptase 1 function. Consistent with this dual role, downstream of PLD, the Matriptase transduction pathway splits into an oncogenic and a tumor-suppressive branch, the latter involving sphingosine-1-phosphate (S1P)-dependent apical cell extrusion. Via this means, not only outer peridermal cells, but also (transformed) basal keratinocytes entosed by