Graduate School Event

Thesis Defense: HUMAN MICROGLIA IMPACT NEURONAL DEVELOPMENT IN RETINAL ORGANOIDS

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Prenatal immune challenges pose significant risks to human embryonic brain and eye development. However, we still lack knowledge about the safe usage of anti-inflammatory drugs during pregnancy. Human induced pluripotent stem cell (hIPSC)-derived brain organoid models provide a unique opportunity to investigate neuronal development and have started to explore functional consequences upon viral infection. However, brain organoids usually lack microglia, the brain-resident immune cells which actively participate in neuronal development. At the same time, microglia are known for their immune-sensing properties and will contribute to viral-mediated effects. In my thesis, I investigated the multifunctional roles of human microglia during retinal development and explored their potential contributions to the consequences of viral infections.First, we characterized the innate occurrence of IBA1+-microglia-like cells within the retinal organoid differentiation (Bartalska et al., 2022). Therefore, we differentiate hIPSC using an unguided retinal organoid differentiation protocol and observe that innately developing IBA1+-cells enrich in mesenchymal over retinal structures. To enrich for IBA1+-microglia precursors (preMG), we guided the differentiation with a low-dosed BMP4 application. We characterized preMG for their microglia-like identity and validated their functionality. Next, we assemble preMG into 3D-retinal organoids and observe that microglia-like cells (iMG) populate the outer plexiform layer once it forms (Schmied et al., 2025). However, at this developmental stage, the ganglion cell number decreases in 3D-retinal organoids. Thus, we adapted the model into 2D which promotes their survival. Integrated iMG engulf ganglion cells and control their cell number. In parallel, we apply the immunostimulant POLY(I:C) to mimic a fetal viral infection. Although POLY(I:C) stimulation affects iMG phenotype, it does not influence their interaction with ganglion cells. Furthermore, iMG presence significantly contributes to the supernatant's inflammatory secretome and increases retinal cell proliferation. Simultaneous exposure to the non-steroidal anti-inflammatory drug (NSAID) ibuprofen dampens POLY(I:C)-mediated consequences of the iMG phenotype and ameliorates cell proliferation. Remarkably, while POLY(I:C) disrupts neuronal calcium dynamics independent of iMG presence, ibuprofen rescues this effect only in the presence of iMG. Mechanistically, ibuprofen blocks the enzymes cyclooxygenase 1 and 2 (COX1/ PTGS1 and COX2/ PTGS2) simultaneously, from which iMG predominantly express COX1. Selective inhibition of COX1 does

not restore the calcium peak amplitude upon POLY(I:C) stimulation, indicating ibuprofen's effect depends on the presence and interplay of both, COX1 and COX2. In summary, our results underscore the importance of microglia during neurodevelopment, in the context of prenatal immune challenges and provide insight into the mechanisms by which ibuprofen exerts its protective effects during embryonic development.

Monday, June 16, 2025 01:30pm - 02:30pm

Office Bldg West / Ground floor / Heinzel Seminar Room (I21.EG.101) and Zoom

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