Participation Report

Participant: Germán Camargo Ortega, Helmholtz Zentrum München, AG Magdalena Götz
Venue: Join Keystone Symposia Neurogenesis during Development and in the adult brain and Transcriptional and Epigenetic Control in Stem Cells
Place/Date: Resort at Squaw Creek, Olympic Valley, California, USA, January 8-12, 2017

Various novel highlights

Sebastian Jessberger (University of Zürich, Switzerland) interrogated the behavior of hippocampal adult neural stem cells (aNSCs) and their progeny. For this, he used in vivo life imaging combined with single cell fate mapping. Briefly, he could observe that aNSCs are not long-term self-renewing; instead, they continuously self-renew 5-7 times asymmetrically until exhaustion. The output of self-renewal was one NSC and a neuronal or an astroglial precursor. In average, however, the last two rounds of division gave rise exclusively to neurons. Direct differentiation of aNSCs to a neuron was also observed. Importantly, this behavior is similar in aNSCs of the subependymal zone (see Calzolari et al. 2013, Nat Neursci).

Kinichi Nakashima (Kyushu University, Japan) asked which of the many roles of MeCP2 is responsible for the phenotypes observed in Rett Syndrome (RTT; MeCP2 loss-of-function) (i.e. autism, mental retardation, bigger brains, neurons with decreased soma, gliogenesis at the expense of neurogenesis). He described a regulatory mechanism of multiple layers, briefly: MeCP2 positively regulates the expression of many miRNAs, among them miR199a. MiR199a loss- and gain-of-function mimics the effects of MeCP2. Smad1-mRNA (BMP signaling) is a target of miR199a and in both MeCP2- and miR199-LOF Smad1-mediated signaling is over-activated. RTT-symptoms (MeCP2 KO-mouse) are ameliorated by miR-199a overexpression or block of Smad1 signaling.

Gou-Li Ming (Johns Hopkins University, USA) is interested in understanding how Zika virus (ZIKV) affects neurogenesis. She makes use of hiPS cells- derived cerebral organoids. Her organoids were derived using the protocol by Lancaster et al., 2013 (Nature) in miniaturized spinning reactors developed in her lab. This allowed in one hand forming organoids with different neuronal layers resembling a real neocortex and in the other hand scaling-up the procedure, which is useful in the context of drug screening. Indeed, she mentioned that thanks to these improvements, she discovered two candidate drugs that inhibit viral infection and block of ZIKV-induced neural progenitor cell death. Furthermore, in trying to understand the infection mechanisms of the virus, she found ZIKV-NS2A protein binds to adherens junction (AJ) proteins such as beta-Catenin and that NS2A overexpression (which would mimic a viral infection) leads to a break of the AJ-belt in neural progenitors of cerebral organoids and of the mouse developing forebrain. This results in proliferation defects in progenitor cells.

Scientific interactions

Talk at poster session with many experts in (neural) stem cell and developmental biology (e.g. Arnold Kriegstein (San Francisco), Kat Hadjantonakis (New York), Armen Saghatelyan (Quebec), Jürgen Knoblich (Vienna)). Discussion was mainly focused on the role of the novel centrosomal protein Akna (my project) in the developing brain and implications in ciliogenesis. I explained how Akna regulates microtubule (MT) organization in neural stem and progenitor cells and how is this important for delamination and neuronal migration. I also discussed that gain or loss of function of Akna does not affect ciliogenesis. People at the poster suggested checking the function of Akna and MT organization in other cell types and in different contexts such as somatic cell reprogramming. A very positive result of scientific interaction is our future collaboration with the Saghatelyan lab, to check Akna's function in migration of neuroblasts during adult olfactory bulb neurogenesis.

I have a second project on the role of lncRNAs and miRNAs mediated regulation of transcription in neurogenesis. Interactions with experts in epigenetic control were, therefore, also very intense. Dialog

was centered on the different ways lncRNAs could positively and negative regulate expression of neighboring genes, including miRNAs, and the significance of this type of regulatory axis. I had the opportunity to talk with scientist whose gene of interest are/would be regulated the miRNA I am currently studying. We discussed collaborative work with one groups at the Johann Wolfgang Goethe-Universität Frankfurt am Main and another group at Friedrich-Alexander-Universität Erlangen-Nürnberg.

Personal experience at the symposium

The symposium offered a good opportunity to get an up-date about the latest advances in neurogenesis and neural stem cell biology. The fact that it was a joint symposium on transcriptional and epigenetic control of stem cells allowed for cross-disciplinary discussions and exchange of ideas and perspectives in general stem cell biology. In general, however, from my point of view, there was no report on a mayor scientific breakthrough, if compared for example with the development/discovery of iPS-cells or CripsprCas9. There was rather a strong focus about the applications of human iPS cell-derived cerebral organoids to mimic human neural development, neurological diseases and as tool for drug-screening. Yet, one could say that although many labs have reported that brain organoids can form even a layered-neocortex-like structure, none of them showed formation of inner and outer subventricular zone. Importantly, these two zones are the characteristic feature of developing gyrencephalic brains, including humans. Thus, faithful recapitulation of normal human brain development in a 3D model in vitro requires still the ability to generate an enlarged subventricular zone.

As a last-year PhD student, visiting the symposium was extremely helpful because I was able to observe and approach stem cell researchers and discuss about future post-doctoral period in their laboratories.