Open position for the LSM call of applications

Department/Institute: LMU Faculty of Biology, Neuroscience

Subject areas/Research fields: Neuroscience

Keywords: Mouse Models, Neurodevelopmental Disease, Microtubules

Name of supervisor: Prof. David Keays

Project title: The Role of the MAST Genes in Development and Disease

Project description:

Background.

The development of the human brain requires the precise orchestration of multiple cellular events that are highly dependent on the microtubule cytoskeleton. During mitosis microtubules are required for the separation of sister chromatids, facilitating the faithful transfer of genetic information from one cell to another. As they exit the proliferative ventricular zones microtubules provide the necessary force to translocate the nucleus, and mediate changes in cell architecture as the nascent neuron adopts a bipolar morphology. Once a cell arrives at its anatomical destination microtubules play a critical role in neuronal differentiation, facilitating axonal extension and the formation of large white matter tracks such as the corpus callosum. The identification of de novo and inherited mutations in genes that encode for tubulins and microtubules associated proteins in patients with severe neurodevelopmental disorders underscore their critical role microtubules play in brain development (Kielar et al., 2014). More recently, we have shown that mutations in an uncharacterised microtubule associated serine threonine kinase (MAST1) causes mega-corpus-callosum syndrome with cerebellar hypoplasia and cortical malformations (MCC-CH-CM) (Tripathy et al., 2018).

The Microtubule Associated Serine/Threonine (MAST) family of kinases consists of four enzymes (MAST1-4) that are members of the AGC protein group (Manning, 2002, Pearce et al., 2010), that were first cloned from brain, testicular and muscle cDNA libraries. They share a similar domain structure comprised of a domain of unknown function 1908 (DUF1908), a kinase domain, and a scaffolding PDZ domain and homologues are found in vertebrates, insects and yeast. The human MAST1 is 1570 aa in length and contains three conserved domains: the domain of unknown function (duf) 1908, a kinase domain, and a PDZ domain, which acts as scaffolding domain (Figure 2). Murine Mast1 has been found to associate with microtubules in a MAP-dependent manner and is primarily expressed in postmitotic cortical neurons of the developing brain[12]. The molecular function of MAST proteins are not known. This project will involve the characterisation of a new MAST mouse model, with the goal of understanding the molecular and cellular mechanisms that underlie the disease state.

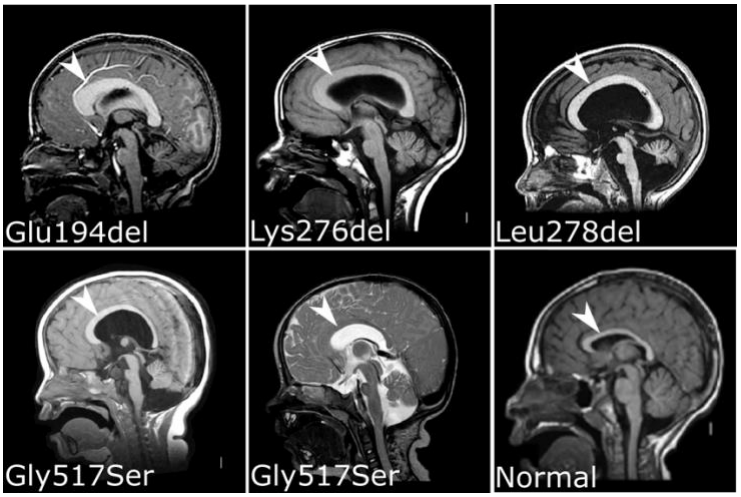

Figure 1: Patients with MAST1 mutations. Magnetic resonance images of five MCC-CH-CM patients and a healthy patient in the midline sagittal plane. The corpus callosum is indicated (arrowheads). The specific MAST1 mutations are shown. Adapted from: Tripathy et al. 2018.

Hypothesis.

We hypothesize that MAST mutations:

1) Perturb the assembly, stability and/or dynamics of microtubules;
2) Microtubule dysfunction disrupts axonal and neurite formation during neurodevelopment.
3) Incorrect neuronal circuit formation results in severe epilepsy and intellectual impairment.

Methods

Characterisation of mouse models, Cerebral Organoid Generation, iPSC culturing, CRISPR-Cas9 genome engineering, histological analysis, imaging.

References:

Tripathy, R., Leca, I., van Dijk, T., Weiss, J., van Bon, B. W., Sergaki, M. C., Gstrein, T., Breuss, M., Tian, G., Bahi-Buisson, N., Paciorkowski, A. R., Pagnamenta, A. T., Wenninger-Weinzierl, A., Martinez-Reza, M. F., Landler, L., Lise, S., Taylor, J. C., Terrone, G., Vitiello, G., … Keays, D. A. (2018). Mutations in MAST1 Cause Mega-Corpus-Callosum Syndrome with Cerebellar Hypoplasia and Cortical Malformations. *Neuron*, *100*(6), 1354-1368.e5. https://doi.org/10.1016/j.neuron.2018.10.044

Spinelli, E., Christensen, K. R., Bryant, E., Schneider, A., Rakotomamonjy, J., Muir, A. M., Giannelli, J., Littlejohn, R. O., Roeder, E. R., Schmidt, B., Wilson, W. G., Marco, E. J., Iwama, K., Kumada, S., Pisano, T., Barba, C., Vetro, A., Brilstra, E. H., van Jaarsveld, R. H., … Carvill, G. L. (2021). Pathogenic MAST3 Variants in the STK Domain Are Associated with Epilepsy. *Annals of Neurology*, *90*(2), 274–284. https://doi.org/10.1002/ana.26147;

For further information, please contact: Keays@bio.lmu.de

Research group website: Keayslab.org

Apply: Please send your application through the online portal of the Graduate School Life Science Munich (LSM).