3 years PhD student position in Neurobiology

Deciphering dendritic spine mechanobiology during synaptic plasticity using super-resolution microscopy

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Project Summary

The dendritic spine is a small protrusive structure that is made of a head and a narrow neck emerging from the dendritic shaft. This structure is crucial for neuronal physiology as it is where the postsynaptic compartment of most excitatory synapses is localized and its peculiar shape allows for specific micro-compartmentalization of neuronal signaling. Spine morphology is very plastic; spine head and neck sizes correlate almost perfectly with synaptic strength and spines grow or shrink during synaptic potentiation or depression, respectively (Nakahata, Frontiers in Synaptic Neurosciences 2018). Importantly, the molecular composition and the correlated morphology of spines are critical for synaptic function. Mechano-sensing is emerging as a key mechanism regulating neuronal functions during physiological processes, including neuronal development (Koser, Nature Neurosciences 2016) and synaptic transmission (Ucar, Nature 2021). Despite the fact that they probably involve adhesion and cytoskeleton proteins, the molecular mechanisms underlying neuronal mechano-sensing remain unknown**.** The overarching objective of this PhD project addresses this precise fundamental question.

In collaboration with the group of Gregory Giannone (IINS), different methods to deform spines by applying external mechanical forces will be used (global neuron stretching, local substrate deformations principally). Their impacts on spine shape, mechanical stability and synaptic transmission will be studied by a combination of molecular tools, electrophysiology and state of the art imaging methods, including super-resolution microscopy (STORM, PALM, STED) but also FRET-based force sensors imaging.

As a first molecular target for mechanical regulation/transduction of dendritic spines, the PhD student will study the role of a major class of cytoskeletal protein called β spectrins. Spectrins have actin-binding domains at their ends and various membrane-interacting sites along their length. Spectrin's functions are best characterized in erythrocytes, where the 2D membrane-bound actin-spectrin network maintains the biconcave cell shape and provides mechanical support. Spectrins are also present in other cells and are especially important for the nervous system (Bennett, Cold Spring Harbor perspectives in biology 2009). In fact, several pathogenic variants have been recently described in central nervous system diseases including developmental delay and autistic features (Cousin, Nature Genetics 2021). The emergence of super-resolution microscopy in the

past years uncovered the peculiar organization adopted by actin and β spectrins in neurons at the nanoscopic level. A ring-like actin-spectrin network structure appears in axons with 180–190nm periodicity (Xu, Science 2013). A similar periodic pattern in patches of dendrites and in spines has been described and is under detailed characterization in the team. The team already demonstrated that spectrin removal leads to a drastic reduction of dendritic spine number and prevents dendritic spine shape changes during synaptic plasticity. Interestingly, β spectrin is composed of specific domains unfolding upon mechanical forces, as demonstrated for proteins involved in mechano-sensing and mechano-transduction. This led to the hypothesis that the ring-like actin-spectrin network may have a mechano-protective or even a mechano-transduction role during synaptic plasticity (Hammarlund, Journal of Cell Biology 2007; Krieg, Nature Cell Biology 2014).

The PhD student will now investigate the impact of spectrin perturbations on dendritic spine mechanical and functional behavior. To this aim, the candidate will take advantage of the construction and validation by the team of several β spectrin mutants and CRISPR/CAS9 methods to generate KO neurons. The impact of these perturbations will be investigated with the experimental approaches described above.

Environment

The PhD student will benefit from cutting edge facilities and interdisciplinary scientific environment. In particular, Anna Brachet in Choquet's team scientific and technical knowledge on dendritic spine biology (Brachet, Cell Report 2021, Brachet, JCB 2015), Giannone's team expertise on mechanobiology and the cytoskeleton (Massou, Nature Cell Biology 2020; Chazeau, EMBO Journal 2014), IINS facilities (Cell Biology, Molecular Biology) and the Bordeaux Imaging Center will be instrumental for this project.

The PhD student will be encouraged to present their data in international meetings.

Qualification and offer

We invite applications from motivated young scientists from all over the world. Applicants should hold a Master's degree or equivalent in Neurosciences or Cell Biology.

Within the frame of the MorphoSpectrin project funded by the ANR, this position is available for 3-years, with a flexible starting date around October 2022. The salary is in accordance with University policy.

Please send your CV, a cover letter with a description of your research interests and two references to: anna.brachet@u-bordeaux.fr

IINS web site: http://www.iins.u-bordeaux.fr/