Institut Pasteur de Lille International PhD Program 2023

Project title:
Role of mechanical signaling in synaptic plasticity and its relevance to Alzheimer's disease

Laboratory:
Inserm U1167 – Risk Factors and Molecular Determinants of Aging-related Diseases

Team:
Molecular Determinants of Alzheimer's Disease and Related Disorders

Thesis director:
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Summary of the proposed project:
Chemical synapses of the nervous system form the basis of learning and memory. Their regulation is a key factor in understanding neuropathological processes leading to cognitive decline and dementia. Accordingly, synapse loss due to the disruption of neuronal plasticity mechanisms is an early event in the Alzheimer's disease (AD) pathogenesis. Synapses undergo activity-dependent structural change, which involves a number of mechanically-relevant processes, including cytoskeleton and cell adhesion molecules (CAMs) (doi.org/10.3389/fncel.2018.00483). Moreover, recent functional screenings of AD genetic risk factors highlighted the focal adhesion pathway for its potential involvement in AD molecular mechanisms (doi.org/10.1007/s00401-019-02004-0). However, little is known about the mechanical aspects of synaptic plasticity, and if and how AD genetic risk factors are involved therein. This project aims to discover mechanically-induced signaling pathways downstream of synaptic CAMs –notably, APP– and to evaluate their respective roles in synaptic plasticity in physiological and AD pathophysiological contexts. To this end, we will first develop a high-content screening to identify the modulators of synaptic CAM mechanotransduction by combining microfluidics, magnetic tweezers, and a battery of biosensors and probes. We will then functionally validate identified pathways in microfluidic neuron culture devices (doi.org/10.1093/braincomms/fcaa139) integrated with microelectrode arrays. We will further characterize these pathways by modulating the expression levels of AD risk genes that are known to modulate synapses and AD-related synaptotoxicity. This is an ambitious project at the intersection of neurodegenerative diseases and mechanobiology fields that deals with an emerging yet understudied concept using custom, innovative tools.