Thesis Project

Dynamics and organelles interplay in neuronal physiology

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Organelles are intracellular compartments whose activities must be coordinated. However, the spatial and temporal organisation of the different organelle populations, particularly in neurons, and the way in which this is controlled by physiological or pathological factors remain enigmatic. In particular, peroxisomes (PERs) are organelles that perform important functions in oxidative and lipid metabolism. A dysfunction of their metabolism is the cause of serious developmental brain abnormalities, and multiple lines of evidence indicate that their malfunction may also be involved in the etiology of psychiatric and neurodegenerative diseases. The proper functioning of PERs involves close physical and biochemical interactions with the mitochondria (MITO). These interactions, which condition their metabolism, require an adequate relative positioning achieved through their intracellular transport along microtubules and actin via specific molecular motors. This transport allows their precise positioning in different territories of the cell according to metabolic needs. We do not know whether the dynamics of the PER-MITO relations are controlled by synaptic activity. In particular, we do not know whether the transport and relative positioning of PERs and MITOs are controlled by synaptic activity and specific signalling pathways. Conversely, we do not know whether the PER-MITO dialogue is necessary to sustain the energy demand associated with synaptic transmission and plasticity processes and memory formation. This thesis project aims to demonstrate that synaptic activity determines the transport of specific populations of organelles and thus their interaction on which their metabolism depends and that, conversely, this communication between organelles is vital for synaptic plasticity and cognitive functions in the long term. Our ambition is to describe the molecular mechanisms and physiological conditions that guide these relationships. This is a fundamental question about the role of organelle interaction in brain function and this project will transform our knowledge of the basic principles of synaptic plasticity and offer possibilities for new molecular diagnostics and therapeutic interventions for psychiatric and neurodegenerative diseases as well.