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Interactions neurogliales en physiopathologie cérébrale / *Neuroglial interactions in cerebral physiopathology*

Centre interdisciplinaire de recherche en biologie (CIRB)

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BIOLOGIE STATISTIQUE / *STATISTICAL BIOLOGY*

Responsable : Olivier RIVOIRE

RECHERCHE

Page web : <https://www.college-de-france.fr/site/en-cirb/rivoire.htm>.

Notre équipe cherche à comprendre les principes sous-jacents aux capacités d'adaptation des systèmes biologiques. Notre approche est inspirée de la physique statistique et combine des analyses de séquences génomiques, des expériences quantitatives *in vitro* et des modèles mathématiques. Nos projets actuels sont organisés autour de trois systèmes modèles : les anticorps, les protéases et les génomes bactériens.

Nos résultats récents comprennent le développement de méthodes statistiques pour étudier la co-évolution dans les séquences de protéines et de génomes, le développement d'expériences d'évolution d'anticorps par la méthode de phage *display* et le développement de modèles mathématiques d'évolution de populations sujettes à des environnements fluctuants.

PUBLICATIONS

MAYER A., MORA T., RIVOIRE O. et WALCZAK A.M., « Transitions in optimal adaptive strategies for populations in fluctuating environments », *Physical Review. E*, vol. 96, n° 3-1, 2017, 032412, DOI : 10.1103/PhysRevE.96.032412.

JUNIER I., FRÉMONT P. et RIVOIRE O., « Universal and idiosyncratic characteristic lengths in bacterial genomes », *Physical Biology*, vol. 15, n° 3, 2018, 035001, DOI : 10.1088/1478-3975/aab4ac.

INTERACTIONS NEUROGLIALES EN PHYSIOPATHOLOGIE CÉRÉBRALE /
NEUROGLIAL INTERACTIONS IN CEREBRAL PHYSIOPATHOLOGY

Responsable : Nathalie ROUACH

RECHERCHE

Page web : <https://www.college-de-france.fr/site/en-cirb/rouach.htm>.

The main goal of our group is to determine whether and how the underexplored glial cells, which are the very abundant non neuronal but yet active cells of the brain, play a role in brain information processing. We investigate the molecular modalities and functional outcomes of neuroglial interactions in physiological and pathological conditions, focusing *ex vivo* or *in vivo* on neuronal excitability, synaptic transmission, plasticity and synchronization, as well as on cognitive functions. To do so, we use a

multidisciplinary approach combining electrophysiology, imaging, behavioral testing, mathematical modeling, and molecular tools acting selectively on astrocytes in mice and human tissues.

Using this strategy, we primarily investigated in the last year the role of astrocytes in network activity in normal and pathological conditions as well as the mechanisms underlying astroglial regulation of synaptic function. In particular we explored the impact of several factors on neurotransmission, including (1) pannexin 1 (Px1) channels, (2) Cx30-dependent mechanism underlying astroglial plasticity during development (1). In this context, we also developed a novel approach to study astroglial structural plasticity (3).

We found that Px1, a protein homolog to connexins and which forms membrane channels, controls seizure generation in human cortical post-operative tissues from epileptic patients and in a mouse model of temporal lobe epilepsy (Dossi *et al.*, 2018). Px1 channels are indeed strongly activated in ictogenic condition and contribute to seizures by promoting and sustaining ictal activity. Such control occurs in tissues from epileptic patients with different pathologies and developmental profiles and is mediated by ATP release and activation of P2 receptors. These data suggest that Px1 may be a therapeutic target against various human epilepsies.

Similarly, we found that energy metabolism plays a key role in epileptic seizures. We indeed found that combining nutritional strategies with a low [fat]:[proteins + carbohydrates] protects against seizures to the same extent as the ketogenic diet, a well-established non-pharmacological treatment known to be effective in reducing seizure frequency in pharmaco-resistant patients, but which is however extremely restrictive and can be associated with complications caused by the high [fat]:[carbohydrate + protein] ratio (Dallérac *et al.*, 2018). These results provide evidence that low-fat dietary strategies more palatable than the ketogenic diet could be useful in epilepsy.

We also recently revealed that Cx30, one of the two astroglial gap junction channel subunit, which is a determinant of astroglial synapse coverage controlling synaptic efficacy and hippocampal-based memory via an unprecedented non channel function controlling the astroglial coverage of synapses (Pannasch *et al.*, 2014), also controls the morphology and polarity of migrating astrocytes during postnatal development via its non-channel function (Ghézi *et al.*, 2018). We indeed found that Cx30 sets the orientation of astroglial motile protrusions via modulation of the laminin/ β 1 integrin/Cdc42 polarity pathway. Connexin 30 indeed reduces laminin levels, inhibits the redistribution of the β 1-integrin extracellular matrix receptors, and inhibits the recruitment and activation of the small Rho GTPase Cdc42 at the leading edge of migrating astrocytes. In vivo, connexin 30, the expression of which is developmentally regulated, also contributes to the establishment of hippocampal astrocyte polarity during postnatal maturation. This study thus reveals that Cx30 controls astroglial polarity during development.

The plasticity of the cytoskeleton architecture and membrane properties is important for the establishment of cell polarity, adhesion and migration. We developed a novel approach, which combines stimulated emission depletion (STED) super-resolution imaging and atomic force microscopy (AFM), to correlate cytoskeletal structural information with membrane physical properties in live astrocytes (Curry *et al.*, 2017). Using this methodology we illustrate that scratch-induced migration induces cytoskeleton remodeling caused by a polarization of actin and microtubule elements within astroglial cell processes, which strongly correlates with changes in cell stiffness.

The method opens new avenues for the dynamic probing of the membrane structural and functional plasticity of live brain cells. It can also be used to provide new insights into mechanisms of cell structural remodeling during physiological or pathological processes, such as brain development or tumorigenesis.

PUBLICATIONS

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RÉGULATION MOLÉCULAIRE DE LA SYNAPTOGÈNE CHEZ LA SOURIS / MICE, MOLECULES AND SYNAPSE FORMATION

Responsable : Fekrije SELIMI

RECHERCHE

Page web : <https://www.college-de-france.fr/site/en-cirb/selimi.htm>.

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