Meeting Report: NeuroFrance 2023 Marc Oudart Thesis Report
24-26 May 2023, Lyon, France

The aim of my thesis project was to study the local regulation of translation in astrocytes, as a mechanism for cell polarity, which by enabling long and branched processes that contact synapses (perisynaptic astrocytic processes (PAP)) and blood vessels (perivascular astrocytic processes (PvAP)) could regulate physiological functions in the brain.

To reach this aim, I identified proteins associated with astrocytic polysomes that potentially regulate translation, including the RACK1 protein. My work shows that RACK1 is preferentially associated with the Kcnj10 mRNA encoding the KIR4.1 potassium channel.

I then developed a transgenic mouse model in which RACK1 expression is specifically abolished in astrocytes at the adult stage. As a result, in the cortex and hippocampus of these mice, the level of KIR4.1 expression is increased in perisynaptic astrocytic processes, astrocytes are larger and display increased K+ currents, excitatory synaptic transmission is potentiated and neuronal network activity is modified. Finally, molecular mechanism studies showed that RACK1 inhibited kcnj10 translation through its 5'UTR.

After 2021 virtual edition, Neurofrance, a neuroscience-centered meeting organized by the French Neuroscience Society, was held in Lyon, France, from the 24th to the 26th of May 2023. The big convention center close by the beautiful Parc de la tête d'or and the Rhône river welcomed french neuroscientists and from all over the world to attend per day to 3 plenary lectures, 14 symposia, special sessions and 2 poster sessions within 7 different conference rooms.

Before it began, a satellite event on glial cells

Satellite events were also taking place such as the first young glial cell day on the 23rd of May 2023 at the Lyon university near the city center. This event was organized by the French Club of Glial Cells and proposed 4 symposia around astrocytes, oligodendrocytes, microglia and glial cells interactions. Pr. Mikael Simons from Munich gave a plenary lecture on the mechanisms of remyelination in the central nervous system. His work focused on multiple sclerosis and aging mouse models presenting lesions in the myelin and disrupted remyelination. He and his team found an accumulation of cholesterol in these mice because of a disturbed cholesterol pathway. Interestingly, microglia are able to go in the lesions and sense lipid with TREM2. Through TREM2 activation, they were able to increase cholesterol efflux and remyelination from oligodendrocytes.

A symposium on Neuropeptide-induced regulation of astrocyteneuronal networks and behavior

One of the few symposia on glial cells was held on the first day in the afternoon. Of note, 3 speakers were focusing on the neuropeptide, or peptide hormone, oxytocin. The oxytocin is produced by the hypothalamus and regulates several behaviors such as social interaction, reproduction and emotions. Dr. Alexandre Charlet, from the Institute of Cellular and Integrative Neuroscience (INCI) in Strasbourg discussed about the involvement of astrocytes in oxytocin-induced modulation of fear. Oxytocin receptors (OTR) are present on neurons in the amygdala, the brain area of emotions. However, OTR are also present on astrocytes. Interestingly, OTR+ astrocytes are bigger than OTRastrocytes, suggesting their possible role in controlling neuronal transmission in that area. Indeed, a selective knock-out of OTR in astrocytes did not elicit neuronal response after oxytocin release via optogenetic tools. In addition, no learning based on fear conditioning protocol could be performed in astrocytic-OTR KO mice compared to controls. Next, it seemed that there was a link between oxytocin and astrocyte morphology that remains unclear. Indeed, upon fear conditioning or oxytocin release, astrocytes displayed less contact with synapses. In OTR-KO mice, no morphological changes could be identified in these paradigms.

Laura Boi, from the university of Regensburg, Germany, also studied the link between oxytocin and astrocytes. She focused on the relationship between astrocyte morphology and oxytocin and found that gap junctions proteins specific to astrocytes, connexin 43 were involved. Indeed, the morphological changes induced by oxytocin were abolished when connexin 43 was knocked-out.

Finally, Dr. Nathalie Rouach from the College de France, Paris, France, studied the role of oxytocin and astrocytes in the maternal behavior. She studied oxytoxin effect on astrocytes in the supraoptic nucleus (SON) of the hypothalamus involved in oxytocin secretion. In a maternal behavior experiment, virgin females are exposed with pups increasing oxytocin levels in the SON. She showed that after the pup exposure and oxytocin increase, the process of astrocytes near synapses retracts to allow neurons to fire in the SON. Connexin 30 levels were also shown to decrease. Interestingly, in connexin 30 KO mice, the coverage of these processes in the SON decreased and maternal behaviors and care increased. Finally, she tried to narrow down the mechanism behind the morphological changes by investigating the different functions of connexin 30. By mutating the channel function of connexin 30, she found similar results on maternal behavior compared to wild type mice showing that the non-channel function of connexin 30 was involved.

A symposium on spreading neurodegeneration

A fascinating subject in neurodegeneration has been, how does it propagate in the brain and between multiple cell types? In this symposium, extracellular vesicles (EVs) have been discussed as a mean to propagate aggregated and misfolded proteins. For instance, amyloid beta and C99 as discussed by Dr. Inger Lauritzen at Sophia-Antipolis university, France, are present in EVs and are found to be transferred from neurons to microglia.

Another way to spread proteins between cells is tunnelling nanotubes (TNT). Dr. Chiara Zurzolo at Pasteur Institute, Paris, France, focused on the spreading of amyloid protein via TNT. TNT contain actin, are open ended to connect 2 cells, transport various cargoes and are similar to filopodia, extension of the membrane except that it does not touch the substrate (in vitro). Interestingly, in neurodegenerative paradigms, aggregated proteins increase the formation of TNT to increase propagation for instance of alpha synuclein proteins. Nonetheless, TNT can be in favour of protein aggregates clearing such as the communication between astrocytes and neurons. Neurons can send proteins via TNT to astrocytes (and not the reverse) to degrade these aggregates. TNTs have also been shown between neurons and microglia. An important question raised by Dr. Zurzolo is: does TNT exist in the brain (in vivo)? To tackle this problem, she used connectomics with serial scanning electron microscopy to detect these tiny and fairly rare events. First, she found TNT in vivo between undifferenciated neurons, dividing and migrating cells.

Then, she observed TNT between cerebellar neurons to transfer huntingtin aggregates.

In another symposium, mitochondria and brain cells plasticity in neurodegenerative diseases, Dr. Kevin Richetin, CHUV, Lausanne, Switzerland, discussed about the spreading of tau proteins in EVs in astrocytes to dysregulate mitochondria functions. In Alzheimer's disease, tau protein, a protein associated with microtubules and regulate the transport of organelles such as mitochondria, display a progressive accumulation of the 3R family of tau. Briefly, he found that tau 3R family are present in EVs from patients and that these EVs are derived from neurons are taken up by astrocytes to perturb its mitochondria and increase ROS production and is deleterious for synapses.

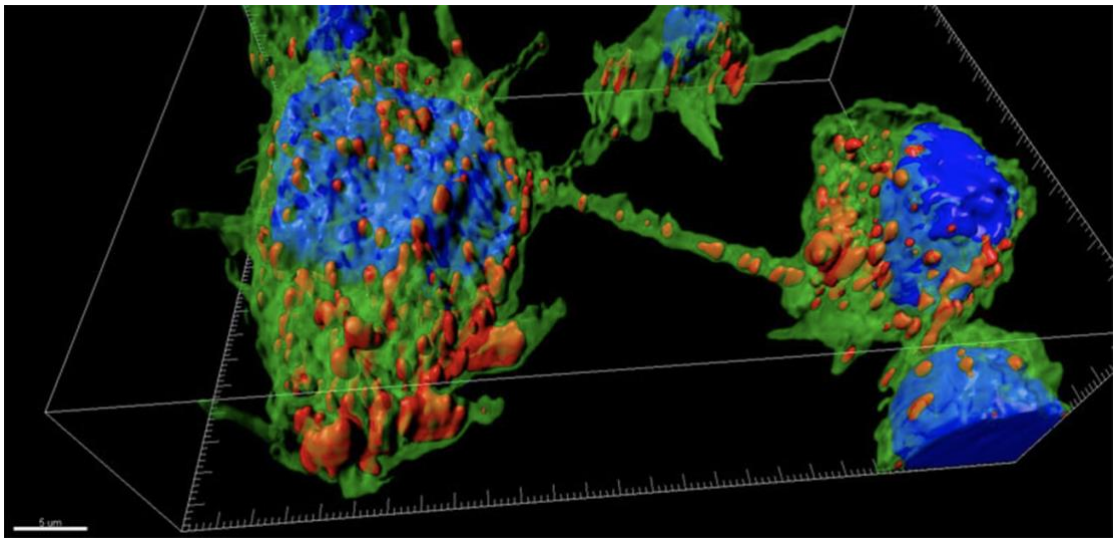

Figure 1: Neuronal cells connected by TNTs which containing synuclein fibrils (aggregates in red) inside. 3D visualization. © Institut Pasteur

A fascinating plenary: The neuroendocrine key to the brain aging enigma

Dr. Vincent Prévot, Lille Neuroscience & cognition, Lille, France, has given a lecture on a misunderstood glial cell called tanycytes. Tanycytes are special ependymal cells along ventricules of the brain and have processes in the hypothalamus. Dr. Prévot and his team found multiple crucial roles for tanycytes. Tanycytes have processes blocking the projection of GnRH producing neurons, an hormone provoking the release of LH and FSH by the pituatary gland in females. When ovulation occurs, tanycytes retract their processes due to Nitrit Oxyde release by endothelial cells and GnRH neurons can project and release GnRH. Another function identified is the regulation of appetite. Leptin and Ghrelin, 2 hormones are secreted in the blood stream. Tanycytes have processes contacting special blood vessels in the brain that are fenestrated. This fenestration allows big molecules to easily pass from the blood stream to the brain parenchyma and is in contradiction of the tight blood-brainbarrier observed in the rest of the brain. Leptin and ghrelin can therefore be

easily sensed by tanycytes via the fenestrations and signal to neurons in the hypothalamus for the regulation of appetite.

Current research of Vincent Prévot and his team is focusing on tanycytes in Alzheimer's disease. They started from a simple statement: In AD, the plasma and cerebro-spinal-fluid (CSF) levels of tau protein increase. However, no one looked at the ratio between plasma and CSF levels. They observed that this ratio was decreased in AD compared to healthy patients. It could mean that the efflux from the brain to the blood is altered. And since they showed inclusions of tau in tanycytes in models of AD, they hypothesized that the transcytosis function of tanycytes in AD is decreased. They looked closely at tanycytes in AD models and found in fact that tanycytes were degraded! Such intriguing discovery can explain that the regulation of crucial hormonal functions is altered in AD such as GnRH secretion problems.

In conclusion, NeuroFrance 2023 was a great opportunity to enrich my knowledge, to discover unpublished data and to discuss with all neuroscientist in France and abroad. The meeting contained plenty of symposia on glial cells in addition to the satellite event. I think this emphasizes the increasing concern to integrate all brain cells in our models and better understand physiology as well as physiopatholgies.

Acknowledgements

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I would like to express my sincerest gratitude to the **French Neuroscience Society** and the **Tianqiao and Chrissy Chen Institute** for awarding me with the prestigious Thesis Prize 2023. This recognition is an immense honor, and I am truly humbled to be selected among such outstanding researchers in the field. This prize holds great significance for my career as it not only validates the countless hours of hard work and dedication I have invested in my research but also highlights the potential impact of my findings. The recognition from the French Society for Neuroscience will undoubtedly open doors to new opportunities and collaborations, enabling me to further contribute to the advancement of knowledge in neuroscience. I am

immensely grateful for their support and encouragement, and I look forward to utilizing this prize as a stepping stone towards an exciting and fulfilling scientific career.