Laboratory rotations

2016-2017

Life and Health Sciences Research Institute
School of Medicine
University of Minho

Post-Graduation

Neurosciences Research Domain

1 Searching for therapies for Machado-Joseph disease.
2 Temporal modulation of the subventricular zone neural stem cell niche by choroid plexus-cerebrospinal fluid.
3 Exploring the Therapeutic Potential of the Secretome of Mesenchymal Stem Cells and Bioreactors in Parkinson's Disease Animal Models.
4 Pharmacotherapies and Extracellular Matrix like Hydrogels as tools for Spinal Cord Injury Regeneration: a combinatory Approach.
5 Modulation of Mesenchymal Stem Cells Secretome through Peptide Grafted 3D Culture Environments: A Focus on Spinal Cord Injury Repair.
6 Sorting Nexin 3 role in neuronal development and behavior.
7 Exploring Sorting Nexin 27 role in Stress.
8 Exploring Sorting Nexin 27 role in Pain.
9 A Poly-pharmacological Therapy to Restore the Injured Spinal Cord.
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12 Regulation of WNT signaling by HOXA9 in Glioblastoma: mechanistic and therapeutic insights.
13 Interplay between HOXA9 and P-Cadherin in Glioblastoma: Functional and Clinical Implications.
14 The role of IL10 in depression and antidepressant treatment.
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16 Asymmetries in rodents' brain function.
17 Asymmetries in human brain function.
18 Social or anti-social? The disruptive power of a peripheral neuropathic lesion.
19 Is memory formation dependent solely on neuronal function? Dissecting the role of astrocytes in cognitive processes.
20 On the role of adult neuro- and glio-plasticity in the healthy and depressed brain.
21 Exploring the role of the transcription factor AP2gamma in the control of post-natal glutamatergic neurogenesis.
22 Drug screening for chronic pain disorders.
23 Stress-driven changes in synaptic interactome: a link between depression and Alzheimer' s disease.
24 Synaptic Tau protein: an unknown target for anesthetics malfunction?
25 Pain-triggered synaptic plasticity: identifying the mechanistic involvement of Tau protein.
26 "Stressed" proteostasis: the chronic stress impact on the orquestration of proteasomal and autophagic pathways in Alzheimer´s disease pathology.
27 Coaching strategies to prevent stress anxiety in test performance.
28 Inflammatory response in AD: the role of interferons.
29 The impact of lipocalin 2 in the central nervous system homeostasis: friend or foe?
30 Behavioral and brain histological characterization of phospholipase D knock-out mice.
31 Stress impact on the brain: neuropsychiatric and physiological consequences.
32 Implication of RNA splicing for Machado Joseph Disease.
33 Functional correlates of adult hippocampal cytogenesis: a matter of sex and time?
34 Immunological aging as a trigger for multiple sclerosis.
35 Exploring the involvement of striatum in the pathology of Machado-Joseph disease: study in a mouse model.
36 Exploring Sorting Nexin 27 role in *Mycobacterium avium* infection.
37 Tau function and dysfunction: characterization of a neuronal cell line.

Skills to be trained in each project are listed in an excel file associated to this document

1

Searching for therapies for Machado-Joseph disease

Summary

Machado-Joseph disease (MJD) is a neurodegenerative disorder caused by the expansion of a polyglutamine (polyQ) tract within the C-terminal of the ataxin-3 protein. Ataxin-3 is known to interact with polyubiquitin chains and to have a deubiquitylase (DUB) activity in vitro, however the cellular and physiological role(s) of this protein remain unknown. The leading hypothesis concerning the pathogenesis of polyQ diseases is that the expanded polyQ tract confers a toxic gain of function to the mutant proteins. These disease proteins acquire the ability to self associate and form aggregates. The lack of therapeutic strategies that effectively prevent neurodegeneration in MJD patients prompted us to search for compounds that modulate mutant ataxin-3 aggregation and neurological dysfunction. Recent data from our lab reveal that many aspects of MJD can be properly modeled in the round worm Caenorhabditis elegans, and others have shown that this animal provides a suitable platform for both the discovery of new bioactive compounds and therapeutic target identification. This project is based on the idea that the finding of effective drugs can be accomplished by looking simultaneously at protein aggregation (conformational disorder) in the live neuronal cells, and on its impact on neuronal-regulated behavior of the whole-animal (neurodegenerative disorder). With this in mind, the student will test some small molecules for their ability to prevent or delay the formation of mutant ataxin-3 aggregates by feeding them to our MJD C. elegans model. Additionally, we will address their effect on motor neuron dysfunction by performing motility analysis. The drugs thus identified will in the future be tested in a mouse model of the disease.

Aims

-To evaluate the effect of pharmacological compound(s) on the aggregation of mutant ATXN3, using imaging-based criteria;

-To evaluate the effect of the same compound(s) on mutant ATXN3-mediated motor neuron dysfunction (motility assay).

References

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Supervisors

Andreia Teixeira-Castro and Patrícia Maciel

2

Temporal modulation of the subventricular zone neural stem cell niche by choroid plexus-cerebrospinal fluid derived factors

Summary

With this project we aim at determining the contribution of molecules secreted from the choroid plexus (CP) towards the cerebrospinal fluid (CSF) in the modulation of the subventricular zone (SVZ) neural stem cell population during brain maturation. Lining the lateral walls of the CSF-filled brain ventricles and in the proximity of the CP, the subventricular zone (SVZ) is one of the main neural stem cell niches in the postnatal brain. Several studies suggest that the SVZ functions as a reservoir of progenitor cells for brain repair. Adult neural progenitor cells in the SVZ are derived from radial glia, the embryonic neural stem cells; during development, radial glia generates neurons and glial cells for the assembly of the mature brain. Interestingly, at birth, the lateral wall of the brain ventricles is still comprised of radial glial cells similarly to what is observed in the ventricular zone in early embryonic stages. Then, in the initial postnatal days, radial glia cells are converted into adult neural stem cells; the latter are the neural progenitors at juvenile and adult stages. The mechanism through which this cellular transition occurs and is regulated in such a short time window period is largely unknown. We propose that factors secreted by the CP towards the CSF play a role in this timely transition of brain morphology. In this project we also aim at understanding how adult CP-derived factors impact in the adult SVZ.

Aims

We currently aim at exploring the specific contribution of CP-born CSF molecules in the homeostasis of the SVZ neural stem cell niche by:

Determining the temporal changes in the CP transcriptome in specific milestones of SVZ development (pre-natal, early post-natal and adult);

Study in vitro and in vivo the impact of identified CP-derived proteins/molecules in the SVZ; in vitro by using a transwell co-culture system of CP epithelial cells and SVZ neurospheres; in vivo with viral vectors that specifically target CP epithelial cells and thus abrogate or overexpression of CP proteins secretion towards the CSF; the impact of this changes in the SVZ is analyzed by using cell specific markers; cell fate of SVZ born cells is analyzed in the olfactory bulb and in the corpus callosum.

References

Falcão, A. M. et al. The path from the choroid plexus to the subventricular zone: go with the flow! Front Cell Neurosci 6, 34 (2012).

Lun, M.P et al. Development and functions of the choroid plexus-cerebrospinal fluid system. Nat Rev Neurosci 16, 445-57 (2015).

Supervisors

João Carlos Sousa and Diana Afonso

3

Exploring the Therapeutic Potential of the Secretome of Mesenchymal Stem Cells and Bioreactors in Parkinson's Disease Animal Models

Summary

Human Mesenchymal stem cells (hMSCs) have been proposed as possible therapeutic agents for central nervous system (CNS) disorders. Nowadays it is suggested that their effects are mostly mediated through their secretome, which contains several neuroregulatory molecules capable of increasing cell proliferation, differentiation and survival (1). In light of the actual knowledge of the MSCs therapeutic potential is extremely relevant to establish the best culture parameters of MSC populations because little is known about the secretome of MSCs and their applications in the CNS (2). Additionally, as MSCs are highly responsive to dynamic culturing environments, one could expect to modulate and possibly increase the level of the above referred neuroregulatory factors in the secretome through the use of bioreactors. Thus, it is logical to hypothesize that when subjected to different dynamic culturing conditions, the secretome of these cells might change. Moreover, as high yields of cells will be obtained, the possibility of having higher concentrations of neuroregulatory factors in their conditioned media (CM) will also increase. We have previously shown that the secretome of MSCs cultured in bioreactors is able to induce higher differentiation rates in populations of human neural stem cells. Following this initial results the goal is to test its therapeutic properties in a Parkinson's Disease rat model. For this purpose the 6-OHDA unilateral model (4) will be used, and the secretome of MSCs locally injected in the striatum and substantia nigra and compared with MSCs and NSCs transplanted groups. Follow up will be assessed trough behavioral and histological analysis.

Aims

Unveil how the dynamic cultured obtained secretome of MSCs modulates: 1) the motor symptoms of PD in the 6-OHDA model; 2) the non-motor symptoms in the 6-OHDA model; 3) Neuronal cell survival and differentiation in the affected areas. Experimental Techniques: Cell and Tissue Culture, Behavioral Analysis, Immunohistochemitry, Histology, Neurostructural Analysis, Fluorescence/Confocal Microscopy.

References

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Teixeira FG et al., Stem Cells Reviews and Reports, 2015, 11(2): 288
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Supervisors

António Salgado and Fábio Teixeira

4

Pharmacotherapies and Extracellular Matrix like Hydrogels as tools for Spinal Cord Injury Regeneration: a combinatory Approach

Summary

Spinal cord injury (SCI) is a major medical problem world-wide that affects 11,000 people/year in EU only and usually results in devastating and permanent loss of function (paraplegia and quadriplegia). Therefore it is urgent to find novel strategies that can lead to the regeneration of SCI affect sites and individuals, as the present ones (mainly pharmacological agents) do not elicit regeneration. Due to the complexity of SCI, only regenerative strategies based on multidisciplinary and integrative approaches such as those presented by tissue engineering concepts, will adequately tackle the problem. Tissue engineering, a field of science that has been developed through the last 15 years, stands on the interface between materials science, biology and medical sciences, and aims at developing tissue hybrids that induce tissue regeneration [1]. By following these concepts we have previously developed extracellular matrix like hydrogels l with enhanced cell adhesion and proliferation properties (mimicking the natural extracellular matrix) [2-4]. The role of the hydrogel is to promote axonal migration, in order to restore the cord's functional properties. Therefore we have modifier it with peptides that are involved in this process, namely GRGRDS (fibronectin) and YIGSR (laminin). On the other hand, while the regenerative step can be fostered by these structures (with or without the combination with stem cells), it is also need to render the injured spinal cord more amenable characteristics for reparative processes to happen, namely by partially inhibiting processes such as inflammation and glial scar formation. Such processes can be achieved by using drugs that target them. Therefore the objectives of this rotation will be to test different combination of drugs and ECM-like hydrogels (with or without cells) and their impact on in vitro and in vivo models of axonal degeneration/regeneration.

Aims and Techniques

Test different combination of drugs and ECM-like hydrogels (with or without cells) and their impact on in vitro and in vivo models of axonal degeneration/regeneration.

Experimental techniques: cell and explant culture; biomaterials modification; immunohistrochemistry; neurostructural analysis; fluorescence/confocal microscopy; in vivo models of SCI; behaviour analysis

References

Langer R, Vacanti J. Tissue engineering. Science. 1993;260:920-6.

- Silva NA, et al. Tissue Engineering Part A. 2010;16:45-54.

Silva NA, et al., Biomaterials, 2012, 33(27):6345-54

Assunção-Silva RC et al., Biomedical Materials, 2015, in press

Supervisors

António Salgado and Nuno Silva

5

Modulation of Mesenchymal Stem Cells Secretome through Peptide Grafted 3D Culture Environments: A Focus on Spinal Cord Injury Repair

Summary

Spinal Cord Injury (SCI) is a chronic condition for which there is still no clinical treatment. In the last decade, the transplantation of Mesenchymal Stem Cells (MSCs) has been suggested as a possible therapy for SCI. This pro-regenerative capacity of MSCs has been linked to the secretion of bioactive molecules that provide trophic support to the damaged tissues, known as the secretome (1,2).

In spite of the aforementioned beneficial roles of MSC transplantation, very low numbers of cells survive within the lesion site, which represents a drawback for their clinical application. A possible alternative is to combine them with biodegradable biomaterials. They can protect encapsulated MSCs, while stimulating the production of growth factors by them, which will enhance the regeneration of SCI (3). Moreover by using peptides from proteins present in MSCs ECM (e.g. fibronectin, laminin and collagen) involved in processes such as cell survival, adhesion and proliferation, to modify these hydrogels, it will be possible to further modulate MSCs secretome, and thus increase the regenerative potential of these cells (4). Thus, it is possible to envision the development of tissue responsive/inductive GG based hydrogels that modulate the action of encapsulated MSCs in the injured spinal cord [11]. The aims of this rotation will be focused on testing a number of different peptides, grafted into hydrogel matrix based on gellan gum, a naturally occurring hydrogel, and assesse their effects on the regenerative potential of MSCs

Aims and Experimental techniques

Test a number of different peptides, grafted into hydrogel matrix based on gellan gum, a naturally occurring hydrogel, and assesse their effects on the regenerative potential of MSCs

Experimental techniques: cell and explant culture; biomaterials modification; immunohistrochemistry; neurostructural analysis; fluorescence/confocal microscopy;

References

Teixeira FG et al., Cellular and Molucar Life Sciences, 2013, 70(20): 3871

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Assunção-Silva RC et al., Stem Cells International, 2015, 948040

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Supervisors

António Salgado and Nuno Silva

6

Sorting Nexin 3 role in neuronal development and behavior

Summary

Protein assembly and turnover abnormalities are hallmarks of several neurodegenerative disorders [1]. The Sorting Nexins family of proteins (SNXs) plays pleiotropic functions in protein trafficking and intracellular signal in neuronal and non-neuronal cells, and has been associated with several human diseases that result from abnormal endosomal function, namely, Alzheimer's disease [2]. Despite the reported roles of SNXs in protein homeostasis in neurodegeneration, not much is known about SNXs function in the nervous system. The aim of this project was to use the nematode Caenorhabditis elegans that encodes in its genome eight SNXs orthologs, and is a reference model organism to study the function and malfunction of the nervous system, to functionally characterize SNXs. We found that SNX3 gene mutation led to an array of developmental defects, namely, reduced brood size, embryonic lethality, delayed hatching, and to a decreased life span. Additionally, SNX3 mutant worms presented distinct behavioral deficits, such as, increased motor uncoordination, impaired chemotaxis and susceptibility to osmotic, thermo and oxidative stresses, which implies perturbed neuronal functions. Altogether, our data supports a prominent role of SNX3 in nervous system development. In this manner, we would like to pursuit with *C. elegans* SNX-3 characterization, by (i) quantifying in the wild-type (WT) worm SNX-3 expression during the developmental cycle (egg to adulthood); (ii) quantifying, in the *snx-3* deletion mutant, the expression level of several receptors and neurotransmitters by qRT-PCR and Western-blot analysis; (iii) microinject the human SNX-3 and SNX-12 genes into the *C. elegans snx-3* mutant background; and (iv) silence SNX-3 expression in the WT worm using siRNA. We will finally perform behavioral characterization of these *snx* mutant worms.

Aims

Characterization of *C. elegans* SNX-3 mutant expression during development.
Evaluate the expression of distinct receptors in the *C. elegans snx-3* mutant background.
Evaluate the behavior of the *C. elegans* snx-3 mutant and of the reintegrated clones (*C. elegans* SNX-3; Human SNX-3 and SNX-12).

References

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Cullen, P.J., Endosomal sorting and signalling: an emerging role for sorting nexins. Nat Rev Mol Cell Biol, 2008. 9(7): p. 574-82.

Supervisor

Neide Vieira

7

Exploring Sorting Nexin 27 role in Stress

Summary

Sorting nexins (SNXs) are a family of proteins that play pleiotropic roles in protein trafficking and that have been associated with endocytic events underlying neurodegeneration, synaptic plasticity and cognition [1-4]. Despite this, not much is known about SNXs role in the nervous system and how their function is modulated by aging, age-related pathologies and stress; conditions that are inextricably linked to endocytic dysregulation, cognitive decline and synaptic malfunction. Previous data from the host lab demonstrated that SNX27 expression is significantly reduced in the PFC (a brain region severely affected by stress exposure [5]) of rats exposed to a mild stress protocol. Interestingly, a C. elegans snx-27 deletion mutant strain displayed an increased susceptibility to heat shock, osmotic or oxidative stresses, which implies a role for SNX-27 in stress tolerance. Taking into consideration the recent findings that SNX27 is tightly associated with Down's syndrome [3] and Alzheimer's disease [6], where its expression is markedly reduced; that stress is a major trigger in neurodegenerative disorders; and that stress-related pathologies display cognitive impairments, synaptic malfunction/atrophy, and decreased proteostasis [7-8], we aim to dissect SNX27 role in stress. For that, SNX27 heterozygous mice (KO mice are not viable) and littermate controls will be exposed to a 6-week Chronic Mild Stress (CMS) protocol. Animals will then be analysed for several behavioral dimensions: locomotion, emotion and cognition. Behavioral assessment will be performed in the following order: elevated plus maze (EPM; anxiety-like behavior), open field (OF; locomotor and exploratory behavior), forced-swim test (FST; depressive-like behavior), working memory water maze (WM; spatial short-term memory), Morris water maze (MWM; spatial reference memory) and spatial reversal (behavioral flexibility). Following behavioral characterization, animals will be anesthetized, CSF samples will be collected, as well as blood serum samples (for posterior analysis of metabolites, cytokines, among others). Tissue samples will also be collected (liver, adrenal glands, thymus, spleen and brain). Half of the brain will then be macrodissected for further RNA or protein analysis, and the remaining brain processed for Golgi staining (for posterior stereological analysis and 3D neuron reconstructions).

Aims

Characterize SNX27 expression by RT-PCR and western-blot analysis in control and stress exposed wild-type and Snx27+/- mice.

Evaluate the subcellular localization and membrane-association of SNX27 in control and stress exposed wild-type and Snx27+/- mice.

Evaluate distinct behavioral dimensions in control and stress exposed wild-type and Snx27+/- mice.

Analyze neuronal volumes, cell numbers and neuronal morphology.

References

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Cerqueira, J.J., et al. Cereb Cortex, 2007. 17(9): p. 1998-2006.

Wang, X., et al. Cell Rep, 2014. 9(3): p. 1023-33.

Powers, E.T., et al. Annu Rev Biochem, 2009. 78: p. 959-91.

Supervisor

Neide Vieira and Susana Roque

8

Exploring Sorting Nexin 27 role in Pain

Summary

Sorting nexins (SNXs) are a large family of phosphoinositide-binding proteins that play fundamental roles in orchestrating cargo sorting through the endosomal network. SNX27 is one of the most studied members of this family and has a well-established role in glutamate receptors trafficking regulation [1, 2]. Glutamatergic transmission is critical for nociception (acute pain) and underlies the onset and maintenance of hypersensitivity in chronic pain conditions [3] but surprisingly, no previous study assessed SNX27 potential as a therapeutical target for pain. Based on this rationale we propose to study the manifestation of acute and chronic pain in a mice model with reduced expression of SNX27. Male SNX27 -/+ mice and littermate controls will be used to assess pain-related behaviors in models of acute noxious thermal (tail- and paw-flick), tonic inflammatory (formalin) and chronic neuropathic pain (spared nerve injury, SNI). In the later, emotional and cognitive behaviors will also be characterized as these are frequently affected in chronic pain conditions [4], using the following paradigms: elevated plus maze (EPM; anxiety-like behavior), open field (OF; locomotor and exploratory behavior), forced-swim test (FST; depressive-like behavior), working memory water maze (WM; spatial short-term memory), Morris water maze (MWM; spatial reference memory) and spatial reversal (behavioral flexibility). Animals will then be anesthetized, spinal cord will be removed for c-fos immunohistochemistry and density estimation. Sciatic nerve ultrastructure will also be studied for g-ratio calculation [axon diameter/ (axon diameter+myelin thickness)]. A- and C-fiber conduction velocity and compound action potential will also be followed.

Aims

Evaluate the impact of decreased SNX27 expression in distinct behavioral dimensions.
Analyze nociception of wild-type and Snx27+/- mice.
Assess Snx27+/- mice tolerance to peripheral neuropathic pain.
Evaluate neuronal volumes, cell numbers and neuronal morphology of wild-type and Snx27+/- mice exposed to SNI.
Quantify spinal cord neuronal activation by c-fos immunostaning in wild-type and Snx27+/- mice exposed to SNI.

References

1.Wang, X., et al., Loss of sorting nexin 27 contributes to excitatory synaptic dysfunction by modulating glutamate receptor recycling in Down's syndrome. Nat Med, 2013. 19(4): p. 473-80.
2.Loo, L.S., et al., A role for sorting nexin 27 in AMPA receptor trafficking. Nat Commun, 2014. 5: p. 3176.
3.Tao, Y.X., J. Gu, and R.L. Stephens, Jr., Role of spinal cord glutamate transporter during normal sensory transmission and pathological pain states. Mol Pain, 2005. 1: p. 30.
4.Leite-Almeida, H., et al., Differential effects of left/right neuropathy on rats' anxiety and cognitive behavior. Pain, 2012. 153(11): p. 2218-25.

Supervisor

Neide Vieira and Hugo Almeida

9

A Poly-pharmacological Therapy to Restore the Injured Spinal Cord

Summary

Spinal cord injury leads to devastating neurological deficits that have a strong impact in the physiological, psychological and social behavior of patients. For these reasons, it is urgent to develop therapeutic strategies that can specifically target this problem. When the spinal cord suffers a mechanical trauma it begins a cascade of cellular and biochemical reactions that leads to further damage. This cascade of reactions, also known as "secondary injury", it is characterized by a strong inflammatory response, glutamate excitotoxicity, release of myelin-derived inhibitors and the formation of a glial scar. These events are known to have a crucial contribution for axon regeneration failure after a SCI. The modulation of the secondary events will most likely play a central role in future clinical therapy. Several authors already demonstrated that the neutralization of a single secondary event leads to some motor recovery and higher neurite extensions in SCI animals. For instance, the modulation of inflammation using demonstrated to promote behavioral and histological improvements in injury rats. Moreover, the administration of Mg or Riluzole revealed to reduce the glutamate excitotoxicity and to promote motor improvements. In addition, the glial scar degradation with has shown to enhance axon regeneration and improve motor function in SCI rat. It was also demonstrated that blocking myelin inhibitory proteins, such as Nogo, MAG or OMgp, facilitates the regeneration of the injured spinal cord. Finally, it was previously shown that the prevention of cAMP hydrolysis stimulates axonal regeneration and motor improvements. These are promising results, however it is missing an integrative approach that combines the activation of growth promoting programs; while at the same time attenuate growth inhibitory pathways and promotes neuroprotection. For this reason, we are studying a poly-pharmacotherapy that can tackle most of the molecular issues responsible for the failure of axon regeneration upon SCI.

Aims

Determination of the bioactivity of the selected drugs when combined into a single pharmacotherapy approach;

Establish a contusion model of SCI in rats.

References

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Supervisor

Nuno Silva

10
Neural circuits of reward and motivation

Summary

Perceiving a rewarding event is so important for species survival as avoiding aversive situations. Reward deficits underlie several neuropsychiatric disorders such as depression, and addiction. Importantly, stress greatly impacts the reward circuit at the molecular and functional level, and acts as a trigger for these disorders.
Characterizing the neural circuits that mediate reward and reinforcement in control and stressed animals is thus important to better understand the etiology of these disorders, and to develop more targeted and efficient therapeutic approaches.

In this work we will use optogenetics to selectively activate/inhibt specific neuronal populations and evaluate its impact in rodent behavior. In addition, we will use electrophysiological tools in order to dissect what is the role of specific neurons in reward-related behavior.

Aims

Optogenetic manipulation/inhibition of specific neuronal populations in reward/motivation-related tasks
Electrophysiological measurements

References

Soares-Cunha C, Coimbra B, Borges S, Pinto S, Costa P, Sousa N, Rodrigues AJ. “Activation of D2 dopamine receptor-expressing neurons in the nucleus accumbens increases motivation”. Nature Communications. (2016)

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Rodrigues, A. J., Leao, P., Carvalho, M., Almeida, O. F., and Sousa, N. “Potential programming of dopaminergic circuits by early life stress”. Psychopharmacology (2010).

Borges, S., Coimbra, B., Soares-Cunha, C., Miguel Pêgo, J., Sousa, N., and João Rodrigues, A.. “Dopaminergic modulation of affective and social deficits induced by prenatal glucocorticoid exposure”. Neuropsychopharmacology (2013).

Supervisor

Carina Cunha & Ana João Rodrigues

11

Linking stress with brain cancer: effects on glioma initiation, aggressiveness and prognosis

Summary

The existence of a clear link between psychological stress and cancer is still a matter of debate. Despite some correlative studies suggesting that stress may influence cancer onset and the prognosis of patients, a truly causative relationship has yet to be shown. This is particularly challenging as stress is not easy to measure objectively, the levels of perceived stress are highly subjective among individuals, and there are different stressors in nature and exposure periods. In this project, we aim to understand the effects of chronic stress in glioma initiation and aggressiveness/prognosis. Gliomas are particularly relevant as the etiologic factors are largely unknown, they are very aggressive cancers for which curative treatments do not exist, and they originate in the brain, where stress induces remarkable alterations. To achieve our goal, and taking advantage of the expertise of many researchers at ICVS, merging the key research areas of neurosciences and oncology, we will induce glioma formation in mice by orthotopic implantation of tumor cells in the brain, and evaluate how the exposure of these mice to established chronic unpredictable stress (CUS) protocols may affect tumor initiation, progression, and mice overall survival. Additionally, the influence of pharmacological approaches that modulate stress-related phenotypes (e.g., cortisol or β-adrenoceptor agonists) in these mice models of glioma will also be tested. After sacrifice, mice brains will be collected for histological and molecular characterization of tumor and surrounding brain tissue. The levels of corticosteroid in the peripheral blood will also be measured and used as a biological correlate of stress.

Aims

Evaluate blood corticosteroid levels and assess putative associations with the survival of mice implanted with glioma.

Evaluate the effect of stress in:

the histological and molecular characteristics of glioma in mice brains;

tumor volume, and lymphatic and blood vessel density within and around tumors.

the recruitment of relevant immune cells into the tumor.

Test if pharmacological approaches (e.g., cortisol or β-adrenoceptor agonists) can modulate stress-related phenotypes, in these mice models of glioma.

References

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Supervisor

Bruno M. Costa and Ana João Rodrigues

12

Regulation of WNT signaling by HOXA9 in Glioblastoma: mechanistic and therapeutic insights

Summary

Glioblastoma (GBM) is the most common and most malignant type of glioma, a heterogeneous group of primary brain tumors. While the clinical outcome of GBM patients is unpredictable, patients are equally treated with a standardized approach. Thus, the identification of new biomarkers is crucial. HOXA9 overexpression in GBM is associated with poor prognosis and a more aggressive tumor phenotype. We recently found that HOXA9 transcriptionally activates components of the WNT pathway. This pathway is hyper-activated in several tumors and associated with cancer stem cell-like features, as well as increased proliferation and therapy resistance. Interestingly, we observed that WNT6, a WNT ligand/activator, is overexpressed in glioma in a grade-dependent manner, and that this overexpression is associated with the poor prognosis of GBM patients. In vitro, WNT6 overexpression was associated with increased viability, invasion, stem cell capacity and resistance to TMZ. In vivo, mice bearing WNT6-positive tumors presented faster glioma-related symptomatology and a significantly shorter overall survival. In this context, we aim to i) understand the molecular mechanisms regulated by Wnt signaling / WNT6 that may contribute to glioma aggressiveness; ii) test novel therapeutic approaches combining the current chemotherapeutic used in the clinics (temozolomide) with an inhibitor of this pathway to improve the therapeutic response of glioma in vitro and in vivo.

Aims

Study intracellular signaling pathways regulated by Wnt6 in glioma (e.g., phosphorylation state of components of PI3K, JNK, and MAPK pathways using phospho-arrays).

Assess the therapeutic potential of a new combinatorial treatment including an inhibitor of the Wnt pathway and temozolomide on glioma models.

References

Supervisor

Bruno M. Costa

13

Interplay between HOXA9 and P-Cadherin in Glioblastoma: Functional and Clinical Implications

Summary

Glioblastoma (GBM) is a highly malignant and the most common primary brain tumor, for which curative therapies are not available. We previously showed that HOXA9, a critical transcription factor during development, is overexpressed in a subset of glioblastoma samples, and is associated with increased tumor resistance to therapy and shorter patient survival. A recent study demonstrated that HOXA9 affects the aggressiveness of ovarian cancer cells by affecting the expression of P-Cadherin, which encodes a transmembrane protein with roles in cell adhesion. Since this HOXA9/P-Cadherin link has not been described in other cancer types, and nothing is currently known on the importance of P-Cadherin in the context of malignant brain tumors, we will study: i) how HOXA9 may affect P-Cadherin levels in glioblastoma; ii) the functional roles of P-Cadherin in glioblastoma, particularly at the levels of cell migration, invasion, viability, and response to chemotherapy; iii) the roles of P-Cadherin in in vivo intracranial models of glioblastoma; iv) the clinical value of P-Cadherin as a prognostic marker in glioblastoma. These approaches will clarify for the first time the relevance of a critical Cadherin in the context of malignant brain tumors.

Aims

-Evaluate P-Cadherin expression in a panel of glioblastoma tumor samples from patients and in cell lines, and correlate them with HOXA9 levels;

-Evaluate how the levels of P-Cadherin influence the aggressiveness of glioblastoma using in vitro models (cell lines) and orthotopic in vivo mice models.

References

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Supervisor

Bruno M. Costa

14

The role of IL10 in depression and antidepressant treatment

Summary

Previous studies from our laboratory showed that female mice lacking IL10 expression show a depressive-like behavior, a phenotype that is rescued by IL10 administration. In accordance, mice overexpressing IL10 present decreased learned helplessness. Interestingly antidepressant treatment, both in patients with depression and in animal models, increases IL10 production. In fact, the reversion of the inflammatory milieu has been shown to play a role for the efficacy of antidepressant treatment. Indeed, treatment-resistant patients have been shown to present a persistent inflammatory profile after antidepressant treatment. In accordance, the concomitant treatment of those patients with antidepressants and anti-inflammatory drugs improved the efficacy of antidepressant therapy. Thus, the goal of this work is to unravel the mechanisms underlying the role of the anti-inflammatory cytokine IL10 in the etiology of depressionand in response to antidepressant therapy. Since two of the most widely discussed mechanisms underlying depression are the altered HPA axis and the imbalance production of cytokines, based respectively, on the frequently observed increased levels of glucocorticoids and pro-inflammatory cytokines in depressed patients, respectively, we will investigate these two mechanisms in mice lacking IL-10 expression. Moreover, preliminary data suggest that IL10KO mice seem to be resistant to antidepressant therapy (both with fluoxetine and imipramine), suggesting that IL10 expression is crucial for the reversion of the depressive-like phenotype. Thus, further studies will be performed to clarify if this animal model could help to better understand the causes of treatment-resistant depression.

Aims

-Assess whether colon inflammation and corticosterone levels could be associated with depressive-like behavior;

-Clarify the role of IL10 in antidepressant treatment

References

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Supervisors

Susana Roque and Margarida Correia-Neves

15

Impact of chronic pain in decision-making - the role of dopamine

Summary

Chronic pain impacts brain structure and function. Indeed, besides sensory abnormalities, chronic pain is frequently accompanied by alterations in emotional and cognitive behavior. The neurotransmitter dopamine emerges here as an interesting link between chronic pain, depression and decision-making as it is individually related with each of these dimensions.

Recently we demonstrated in a rat model of chronic pain that i) chronic pain impacts in a lateralized way decision-making and ii) there are side-specific alteration in the expression of dopamine receptors in the prefrontal cortex and nucleus accumbens, areas involved in decision-making.

In this project we intend to further explore these observations, unraveling the lateralized impact of chronic pain in the dopaminergic system and its posterior involvement in the observed impairments in decision-making.

Aims

Study the impact in decision-making of nucleus accumbens unilateral dopamine depletion;

Manipulate the dopaminergic system unilaterally and study side-specific effects on behavioural readouts in a chronic neuropathic pain model;

References

Leite-Almeida, H., Cerqueira, J.J., Wei, H., Ribeiro-Costa, N., Anjos-Martins, H., Sousa, N., Pertovaara, A., Almeida, A., 2012. Differential effects of left/right neuropathy on rats' anxiety and cognitive behavior. Pain 153, 2218-2225.

Supervisors

Hugo Leite-Almeida and Margarida Cunha

16
Asymmetries in rodents' brain function

Summary
Brain functional asymmetry in a nearly symmetrical body remains paradoxical. Nevertheless, since the 1861's Paul Broca description of a left dominance for language, many side-biased brain processes and behaviors have been described. Such functional asymmetry is not exclusively human; it has also been described in various vertebrate and invertebrate classes, suggesting that laterality is highly conserved across species. The relevance of brain functional asymmetry for cognition and executive function is not understood. For instance, brain imaging studies in older individuals report bilateral activity during the execution of cognitive tasks that in younger subjects were associated with lateralized activity. It remains an open question if the lack of asymmetry is a compensatory mechanism operating from the non-dominant hemisphere and therefore rendering individuals with lower asymmetry functional advantage or if it simply is a correlate of poorer executive function.
The present project proposal is designed to study these questions. We aim to characterize corticostriatal activity in a behavioral paradigm of intertemporal decision-making (impulsivity) and to correlate task-solving efficiency with activity side-biases particularly, its magnitude and directionality (left>right or left<right).

Aims
Characterize trait impulsivity in rats;
Obtain bilateral local-field potentials recordings in relevant areas (e.g. prefrontal cortex) during the execution of the paradigm;

References
Leite-Almeida, H., Guimaraes, M.R., Cerqueira, J.J., Ribeiro-Costa, N., Anjos-Martins, H., Sousa, N., Almeida, A., 2014. Asymmetric c-fos expression in the ventral orbital cortex is associated with impaired reversal learning in a right-sided neuropathy. Mol Pain 10, 41.

Supervisors
Hugo Leite-Almeida and Madalena C. Esteves

17
Asymmetries in human brain function

Summary
Brain functional asymmetry in a nearly symmetrical body remains paradoxical. Nevertheless, since the 1861's Paul Broca description of a left dominance for language, many side-biased brain processes and behaviors have been described. Such functional asymmetry is not exclusively human; it has also been described in various vertebrate and invertebrate classes, suggesting that laterality is highly conserved across species. The relevance of brain functional asymmetry for cognition and executive function is not understood. For instance, brain imaging studies in older individuals report bilateral activity during the execution of cognitive tasks that in younger subjects were associated with lateralized activity. It remains an open question if the lack of asymmetry is a compensatory mechanism operating from the non-dominant hemisphere and therefore rendering individuals with lower asymmetry functional advantage or if it simply is a correlate of poorer executive function.
The present project proposal is designed to study these questions. We aim to characterize both structural and functional hemispheric asymmetries in humans. In order to achieve this we are currently taking advantage of ICVS' large database of MRI and fMRI data from several different cohorts.

Aims
Characterize structural hemispheric asymmetries and find influencing factors;
Determine the importance of functional and structural asymmetries for cognitive function;

References
Corballis MC. The evolution and genetics of cerebral asymmetry. Philos Trans R Soc Lond B Biol Sci 2009;364:867-879.
Sun T, Walsh CA. Molecular approaches to brain asymmetry and handedness. Nat Rev Neurosci 2006;7:655-662.
Toga AW, Thompson PM. Mapping brain asymmetry. Nat Rev Neurosci 2003;4:37-48.

Supervisors
Hugo Leite-Almeida and Madalena C. Esteves

18

Social or anti-social? The disruptive power of a peripheral neuropathic lesion

Summary

Mood disorders are frequently accompanied by alterations in the amount and quality of social interactions. While it is well-established that in experimental models of chronic pain animals develop anxiety- and depressive-like phenotypes, no study has been carried to understand how the social environment contributes to pain manifestation and to the emergence of associated comorbid emotional disorders. Recently, we have observed that in chronic neuropathic pain conditions the rodent's natural ability to interact with an unfamiliar animal conspecific (with or without pain) is disrupted. This proof-of-concept prompted us to further explore these findings. In a series of experiments we will study mutual influences in pain- and mood-related behaviors between cage-mate pairs pain/no-pain, pain/pain and control no-pain/no-pain. Also, social interactions will be studied between familiar and unfamiliar conspecifics in the conditions above. The spared nerve injury (SNI) model of neuropathic pain will be used and putative side-specific effects in left- (SNI-L) or right (SNI-R) –lesions will be analysed as previous studies demonstrated that SNI-L is more anxiogenic than SNI-R. Finally, analgesic pharmacotherapy will be employed attempting to rescue the phenotypes.

Aims

Study mutual influences between cage mates on different conditions of pain
Characterize social behaviour between familiar and (un)familiar animals with and without pain
Study possible lateralized effects of pain (SNI-L vs SNI-R) on social behaviour.

References

Leite-Almeida, H., Cerqueira, J.J., Wei, H., Ribeiro-Costa, N., Anjos-Martins, H., Sousa, N., Pertovaara, A., Almeida, A., 2012. Differential effects of left/right neuropathy on rats' anxiety and cognitive behavior. Pain 153, 2218-2225.

Zhou W, Dantzer R, Budac DP, Walker AK, Mao-Ying QL, Lee AW, Heijnen CJ, Kavelaars A: Peripheral indoleamine 2,3-dioxygenase 1 is required for comorbid depression-like behavior but does not contribute to neuropathic pain in mice. Brain Behav Immun 2015, 46:147-153.

Supervisors

Hugo Leite-Almeida

19

Is memory dependent solely on neuronal function? Dissecting the role of astrocytes in cognitive processes.

Summary

The classical paradigm that brain information processing is exclusively neuronal has been challenged in the past ten years by an exciting body of evidence. Indeed, the importance of glial cells is rising due to emerging data supporting dynamic neuron-glia interactions. These inter-cellular interactions are nowadays widely accepted. Nevertheless, little is known about effects of glial cells, namely astrocytes, in complex behaviour outputs. Astrocytes are able to sense, integrate and respond to neurons. In the lab we have currently mice strains that incorporate genetic modifications to impair specifically each of these 3 functions. The goal of this rotation is to test their performance in cognitive tasks and correlate this performance with electrophysiological or molecular/morphological alterations. This way, the applicant may choose between different approaches to solve the same problem.

By disclosing the net consequence of astrocytic modulation of the neuronal networks we expect to better understand behaviour computation and therefore understand the possible therapeutic approaches in diseases characterized by cognitive dysfunction (e.g. Alzheimer's, Major Depression…).

Aims

-To test the performance of mice with astrocytic dysfunction in working memory and long term memory paradigms (hole board and Morris Water Maze).

-To correlate the performances obtained in the tests with the observed expression of the transgenes in the specific areas by microscopic observation of brain slices containing the targeted areas (prefrontal cortex and hippocampus, respectively), as well as quantification of altered protein levels.

-To analyse the morphological changes in both neurons and astrocytes by means of immunohistochemistry and unbiased stereological techniques.

References

Oliveira JF, Sardinha VM, Guerra-Gomes S, Araque A, Sousa N (2015). Do stars govern our actions? Astrocyte involvement in rodents' behavior. Trends in Neurosciences 38:535–549

M.M. Halassa, C. Florian, T. Fellin, J.R. Munoz, S. Lee, T. Abel, P.G. Haydon, e M.G. Frank, Astrocytic modulation of sleep homeostasis and cognitive consequences of sleep loss, Neuron, vol. 61, Jan. 2009, pp. 213-219

Supervisor

João Oliveira

20

On the role of adult neuro- and glio-plasticity in the healthy and depressed brain.

Summary

Depression is estimated to affect around 20% of the world population and is the leading cause of disability worldwide. Notably, Portugal has one of the highest rates of psychiatric disorders in Europe (22.9%), with anxiety (16.5%) and depressive disorder (7.9%) being the most relevant. Depressive disorder affects all communities across the world and is more prevalent in women than in men (2:1). Despite these striking numbers, the neuropathological basis of depression remains obscure; moreover, about 65% of patients fail to respond to current first-line therapies, making this field of research a top priority.

Thus, the aim of this project is to unveil how hippocampal adult-born (ABAs) and pre-existing astrocytes (Pre-As) control neuroplasticity, neurophysiology and complex behaviors in health and depression. For this, we will use an original and innovative approach to selectively ablate or silence astrogliogenesis and Pre-As by developing an unprecedented genetic tool that will promote targeted cell-death or silencing of ABAs and Pre-As in the adult brain, while not affecting the neuronal lineage. Complemented by other state-of-the-art techniques (optogenetics, neuroimaging), this will allow fine dissection of the relevance of these cells in the remodeling and functioning of neuroglial networks for behavioral control.

This project has the potential to open a new array of therapeutic targets for depression, promoting the re-investment of the pharmaceutical industry in neuropsychiatry and the development of novel therapeutic interventions to treat depression.

Aims

-Determine how ablation/silencing of hippocampal ABAs or Pre-As in the healthy adult brain impacts on brain neurophysiology, neuronal connectivity, and behavior

-Assess the role of hippocampal ABAs and Pre-As for adult brain neurophysiology, neuronal connectivity, and behavior in the context of depression and AD treatment, using a stress-induced rat model of depression

References

Mateus-Pinheiro A, Pinto L, et al., Sustained remission from depressive-like behavior depends on hippocampal neurogenesis. Transl Psychiatry. 2013 Jan 15;3:e210.

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Patrício P, et al., Differential and Converging Molecular Mechanisms of Antidepressants' Action in the Hippocampal Dentate Gyrus. Neuropsychopharmacology. 2015 Jan;40(2):338-49

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Supervisor

Luísa Pinto

21

Exploring the role of the transcription factor AP2gamma in the control of post-natal glutamatergic neurogenesis

Summary

The view of the central nervous system (CNS) as an immutable system in now outdated, and several lines of evidence demonstrate that the CNS is endowed with significant regenerative and neuroplastic potential. In fact, it is now well established that new cells are continuously generated during adulthood in specific brain regions, a process called neurogenesis. The current challenge relies on dissecting the regulatory mechanisms of the adult neurogenic process. Recently, we have identified AP2gamma (AP2) as an important transcription factor involved in developmental corticogenesis. We now seek to explore whether AP2 has a role on the regulation of adult neurogenesis and its importance for different emotional and cognitive modalities.

Aims

Analyze different behavioral and molecular parameters in WT and AP2gamma conditional knockout mice.

Evaluate the impact of AP2gamma deletion on adult hippocampal neurogenesis and neuronal morphology.

References

Pinto L. et al, "AP2γ regulates basal progenitor fate in a region- and layer-specific manner in the developing cortex", Nat Neurosci. 2009 Oct;12(10):1229-37

Supervisor

Luísa Pinto

22

Drug screening for chronic pain disorders

Summary

Chronic pain and depression are enormous health and financial burdens on our society, with depression also being the major comorbidity of chronic pain disorders. Chronic pain induces a profound change in the expression of peptides and their receptors that leads to changes in brain wiring (neuronal plasticity) of central pathways mediating pain [1].

In this work, chronic pain will be induced in Wistar han adult rats for a period of 4 weeks followed by the administration of drugs for an additional 3 weeks. At the end of this period, behavioural analysis to evaluate anxiety- (acoustic startle, open field and elevated plus maze), depressive-like (forced swimming test and sucrose preference test) behaviour as well as nociception [pain behaviour - tail and paw-flick tests (heat noxious stimulation), cold allodynia (acetone test), the Randall-Selitto and the pressure application measurement tests (mechanical noxious stimulation)] will be performed.

At the end of the behavioural task the animals will be sacrificed and brains will be removed for the evaluation of changes in neurotransmitters pathways, either through RT-PCR or immunohistochemistry. Emotional and nociceptive behavioural data will be correlated to the expression of neurotransmitters and its receptors in several areas of the brain involved in pain modulation.

Aim

To evaluate the ability of different types of drugs to reverse the impact of chronic inflammatory pain upon mood disorders in rodents;

To correlate drug efficiency with changes in the neurochemistry of brain areas involved in pain modulation.

References

Neugebauer V, Galhardo V, Maione S, Mackey SC. Forebrain pain mechanisms. Brain Res Rev. 60(1):226-242.

Supervisors

Diana Amorim and Filipa Pinto-Ribeiro

23

Stress-driven changes in synaptic interactome: a link between depression and Alzheimer' s disease

Summary

World Health Organization estimates that the leading cause of mental disability in the coming years will be depression and Alzheimer's disease (AD), raising these two diseases as significant public health problem. Focusing on risks factors of these diseases, previous clinical and experimental studies suggest a causal role of environmental parameters e.g. chronic stress and the subsequent elevation of stress hormones, glucocorticoids (GC), in pathogenesis of depression while recent findings involve stress in the onset/progression of AD. Neuronal atrophy and synaptic failure have been suggested to play an essential role in stress-related pathologies such as depression as well as in AD. Furthermore, important clues of synaptic disruption mechanism(s) previously implicated in pathophysiology of AD have been recently suggested to also contribute in stress-driven brain pathology involving, for the first time, Tau missorting in mechanism(s) of synaptic damage beyond Alzheimer's disease (Pinheiro et al., 2015; Sotiropoulos et al., 2011). Based on the recently suggested role of Tau in synaptic structure and function interacting with NMDA receptors, PSD-95 and Fyn proteins, this project examines the alterations of synaptic interactome underlying stress-induced neuronal atrophy and synaptic loss searching for molecular targets with neuro- and synapto-protective properties.

Aims

Molecular characterization of stress/GC impact on postsynaptic vs extra-synaptic/presynaptic interactome

In vitro and/or in vivo monitoring of intracellular and synaptic trafficking of receptors and related cell signalling under stressful conditions.

References

Pinheiro S., et al., (2015) Mol Neurob, Sotiropoulos et al., (2015) JAD; Kimura et al., (2014) Phil Trans Roy Soc: Biol Scienc; Sotiropoulos I., et al., (2011) J Neurosc; Catania C., Sotiropoulos et al., (2009) *Mol Psychiatry* 14: 95–105; Sotiropoulos I., et al., (2008) *Neurosc Biobeh Rev* 32: 1161-1173.

Supervisors

Ioannis Sotiropoulos and Nuno Sousa

24

Synaptic Tau protein: an unknown target for anesthetics malfunction?

Summary

General anesthetics (GA) are widely used drugs with various clinical applications but many studies report various cognitive problems (some persistent) after GA exposure. Previous studies have shown that different anesthetics induced Tau hyperphosphorylation whereas Tau hyperphosphorylation is related to memory deficits through brain synaptic loss. Based on the recently suggested role of Tau in synaptic structure and function interacting with various proteins such as NMDA receptors (Ittner and Gotz, 2011), we hypothesize that synaptic Tau may have a unique involvement in anesthetics action. First results of this project have shown that NMDA-related anesthetics modifies neuronal structure altering dendritic arborization and synapses in hippocampus accompanied by cognitive impairment in WTs while this effect was attenuated in absence of Tau. Thus, this project aims to clarify the role of Tau and its interaction with NMDA receptors on synaptic mechanisms underlying anesthetic-induced neuroremodeling and cognitive deficits.

Aim

Perform detailed molecular and structural analysis of synaptic cell signalling and synaptic interactome of Tau

References

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Supervisors

Ioannis Sotiropoulos and Hugo Almeida

25

Pain-triggered synaptic plasticity: identifying the mechanistic involvement of Tau protein

Summary

Tau protein hyperphosphorylation and consequent malfunction is a hallmark of Alzheimer's disease pathology; importantly, pain perception is diminished in these patients. In physiological conditions, Tau contributes to cytoskeletal dynamics and in this way, influences a number of cellular mechanisms including axonal trafficking, myelination and synaptic plasticity. While it is known that these cellular processes are also implicated to pain perception, it was just recently that we demonstrated the direct in vivo role of Tau in nociception (Sotiropoulos et al., 2014) showing that Tau-deficient mice display altered pain perception but the the underlying mechanisms remain unknown. Interestingly, Tau has an important role in the post-synaptic density, where, via interaction with Fyn, contributes to NMDA receptor/PSD95 complex formation the latter has also been implicated in nociception (Ittner and Gotz, 2011; D'Mello et al., 2011). Thus, this project will analyze the molecular alterations of pain-stimulated synapses with particular focus on the suggested interaction of Tau with synaptic receptors responsible for synaptic plasticity in both spinal cord and brain

Aims

Monitor the effect of pain stimuli on synaptic TAU phosphorylation;
-Identify the influence of Tau on synaptic plasticity mechanisms (e.g. trafficking of synaptic receptors, interaction with scaffold proteins)

References

Sotiropoulos et al., (2014) Exper Neurol; Ittner and Gotz, (2011) Nat Rev Neurosci; D'Mello et al., (2011) Mol Ther

Supervisors

Ioannis Sotiropoulos and Hugo Leite-Almeida

26

"Stressed" proteostasis: the chronic stress impact on the orquestration of proteasomal and autophagic pathways in Alzheimer´s disease pathology

Summary

Tau aggregation is a common feature in Alzheimer's disease (AD), frontotemporal dementia (FTD) and other tauopathies. Consistent with suggestions that lifetime stress may be a clinically-relevant precipitant of AD pathology, we previously showed that chronic stress and the main stress hormones, Glucocorticoids (GC), trigger Tau aggregation affecting molecular chaperones such as Hsp90 which is known to be involved in both GC signaling and Tau degradation (Sotiropoulos et al., 2015); still, the underlying mechanisms of the above stress/GC effects remain unclear. This project focuses on how stressful conditions converge on cellular mechanisms underlying Tau aggregation in AD brain monitoring tress/GC-triggered downstream degradation mechanisms (proteasome- and lysosome-related ones) mechanisms using both animal and cell culture experimental approaches.

Aims

-Molecular and cellular characterization of ubiquin-proteasome and autophagic pathways under chronic stress and/or GC treatment.

-Clarification of stress/GC-driven molecular mechanisms relating molecular chaperones such as Hsp90 to Tau degradation pathways.

References

Sotiropoulos et al., (2015) J Alz Dis; Sotiropoulos et al., (2011) J Neurosc; Sotiropoulos et al, (2008) J Neurochem

Supervisors

Joana Silva and Ioannis Sotiropoulos

27

Coaching strategies to prevent stress anxiety in test performance

Summary

Modern lifestyle exerts an enormous burden on individuals by pushing towards increasing productivity and longer working hours. This feeling of persistent underachievement, that modern working conditions exert, leads to burnout and stress-related mental disorders such as anxiety. Additionally, workplace environment is often inappropriate to provide a stress-free environment due to poor lighting, temperature or noise conditions.

Higher education is a transition period before students reach the working environment. Students are subjected to increasing periods of work with a progressive focus on autonomy and continuous assessment as mandated by current educational policies. The increasing workload is perceived as stressful and commonly leads to mental disorders and perception that their cognitive performance is bellow their expected standards. This is corroborated by the high prevalence of anxiety disorders among higher education students.

Stress is known to affect an individual's cognitive performance in a biphasic mode. Too little stress impairs adequate performance, increasing with physiological levels of acute stress and followed by a decrease in performance again with prolonged or disproportioned levels of stress. When an individual is exposed to stressful stimuli (physical or psychological), the organism perceives it as a threatening event and mounts an adequate biological and behavioral responses. The main biological agents are the release of cathecolamines, like epinephrine (adrenaline), and corticosteroids (cortisol). The positive effects of acute stress are attributed mainly to the effect of catecholamines while exposure to chronic stress results in repeated activation of the hypothalamic-pituitary-adrenal axis, leading to cortisol secretion, and elevated circulation of pro-inflammatory cytokines, affecting glucocorticoid sensitivity, brain function and behavior.

Assessment is a fundamental phase in the training and certification process that a higher education student is submitted to. It is also one of the strongest stress factors due to the high-stake implications in the academic progress and self-perceived image. Stress is a risk factor for anxiety and may lead to worsening of performance in assessment tasks.

The present proposal will use cohorts of higher education students as a model in order to study the effect of stress/anxiety in the performance of high demand tasks. We intend to correlate stress/anxiety markers with the response pattern in high-stakes exams and develop coaching strategies in order to improve the students' performance.

Aims

Specifically we aim to:

-characterize how anxiety affects medical student's performance in their assessment, correlating basal levels of self-perceived stress with anxiety levels and test performance;

-address potential biological mechanisms underlying the adverse effects of stress/anxiety on cognitive overload and overall performance of high demand tasks. We hypothesize that these effects are mediated by elevations in stress hormones and pro-inflammatory signals during challenging cognitive tasks;

-evaluate if a directed coaching strategy will improve performance in exams by reducing the level of anxiety and/or stress.

References

Davide Carneiro, Paulo Novais, José Miguel Pêgo, Nuno Sousa, and José Neves. Using Mouse Dynamics to Assess Stress During Online Exams. E. Onieva et al. (Eds.): HAIS 2015, LNAI 9121, pp. 1–12, 2015.

Supervisor

José Miguel Pêgo

28

Inflammatory response in AD: the role of interferons

Summary

Alzheimer's disease (AD) is the most prevalent form of dementia. Cognitive decline and the incapacity to form new memories are the major constrains of AD patients. Herein we intend to target cognitive decline by addressing the impact of the levels of interferons (IFNs) on cognitive performance in AD. Here we propose to explore how peripheral and central interferons (IFNs) impact on Alzheimer's disease (AD). Our motivation is triggered by our recent observation of a shift in the expression levels from the IFN type II to type I response during aging, both in the liver and in the choroid plexus of an AD mouse model. In face of publish data and our preliminary results, the present project is biologically relevant in proposing to (i) explore the novel concept that the modulation of peripheral and central IFNs *in vivo* may hamper cognitive decline in AD, and (ii) unravel how IFNs influence pathology, namely in amyloid precursor protein processing/Aβ levels, neurotrophins expression, inflammation and synapse functioning.

Aims

1-Investigate the impact of IFNs, on AD-related cognitive decline and pathology.

2-Determine to what level cognitive impairment is preventable and/or (fully or partially) reversible by targeting central and/or peripheral IFNs.

References

Mesquita SD, Ferreira AC, Gao F, Coppola G, Geschwind DH, Sousa JC, Correia-Neves M, Sousa N, Palha JA, Marques F. The choroid plexus transcriptome reveals changes in type I and II interferon responses in a mouse model of Alzheimer's disease. Brain Behav Immun. 2015 Oct;49:280-92. doi: 10.1016/j.bbi.2015.06.008.

Supervisor

Fernanda Marques

29

The impact of lipocalin 2 in the central nervous system homeostasis: friend or foe?

Summary

Lipocalin 2 (LCN2), an acute-phase protein that, by binding to iron-loaded siderophores, is a potent bacteriostatic agent since it participates in the iron-depletion strategy of the immune system to control pathogens. The recent identification of a mammalian siderophore also suggests a physiological role for LCN2 in iron-homeostasis, specifically through iron delivery to cells via a transferrin-independent mechanism. LCN2 participates, as well, in a wide variety of cellular processes, including apoptosis and proliferation. In the central nervous system, less is known about the processes involving LCN2, namely which cells are producing this molecule or its impact on cell proliferation and death or on emotional behaviours. Importantly, LCN2 has recently emerged as a relevant clinical biomarker, namely in multiple sclerosis; again, there are conflicting views on the role of LCN2 in pathophysiological processes, with some studies pointing to its neurodeleterious effects, while others revealing it as neuroprotective.

Aims

Determine the role of LCN2 in cognition and cell proliferation

References

Ferreira AC, Dá Mesquita S, Sousa JC, Correia-Neves M, Sousa N, Palha JA, Marques F. From the periphery to the brain: Lipocalin-2, a friend or foe? Prog Neurobiol. 2015 Aug;131:120-36. doi: 10.1016/j.pneurobio.2015.06.005

Supervisor

Fernanda Marques

30

Behavioral and brain histological characterization of phospholipase D knock-out mice

Summary

Since lipids are the major constituent of the brain, the modulation of its levels can potentially have an impact in its functioning. One the enzymes that can modulate the levels of signaling lipids is phospholipase D (PLD). Specifically, PLD is responsible for the generation of phosphatidic acid (PA) from phosphatidylcholine. PA is a central signalling lipid with membranar fusogenic properties. Consequently, the modulation of its levels can potentially alter cellular/neuronal functioning.

In mammals there are two main PLD isozymes: PLD1 and PLD2. They both catalyse the same reaction, but they differ in their regulatory properties and cellular location. Thus the genetic ablation of either PLD1 or PLD2 has a differential impact. To date there are only four published studies with PLD knock-out mice, which show a role for PLD1 in platelet functioning and autophagy and the ablation of PLD2 was shown to be protective in a Alzheimer's disease mouse model.

However the precise role of PLD1 and PLD2 in brain functioning is still elusive. We propose to study the impact of both PLD1 and PLD2 ablation in mice cognitive-associated behavior and brain hippocampal organization.

Aims

-To characterize the impact of PLD1 and PLD2 ablation in mice behavior.

-To characterize the impact of PLD1 and PLD2 ablation in mice brain histological organization.

References

-Comparative lipidomic analysis of mouse and human brain with Alzheimer disease. Chan RB, Oliveira TG, Cortes EP, Honig LS, Duff KE, Small SA, Wenk MR, Shui G, Di Paolo G. J Biol Chem. 2012 Jan 20;287(4):2678-88.

-Phospholipase D2 ablation ameliorates Alzheimer's disease-linked synaptic dysfunction and cognitive deficits. Oliveira TG, Chan RB, Tian H, Laredo M, Shui G, Staniszewski A, Zhang H, Wang L, Kim TW, Duff KE, Wenk MR, Arancio O, Di Paolo G. J Neurosci. 2010 Dec 8;30(49):16419-28.

-Phospholipase D in brain function and Alzheimer's disease. Oliveira TG, Di Paolo G. Biochim Biophys Acta. 2010 Aug;1801(8):799-805. Epub 2010 Apr 23. Review.

Supervisor

Tiago Gil Oliveira

31

Stress impact on the brain: neuropsychiatric and physiological consequences

Summary

Stress affects decision-making and prolonged stress exposure can lead to depression, posttraumatic stress disorders and other deleterious health effects. Under stressful situations, glucocorticoids are released by the body to act in the brain, restoring homeostasis and promoting behavioral adaptation. Although this short-term stress is adaptive, long-term stress is clearly associated with disease vulnerability, including mental illness. Despite self-awareness from the affected individuals, the magnitude of stress-response is uncontrollable and the "tipping point" between adaptive and maladaptive stress remains unknown.

How does stress remodels brain activity and switches-off cognitive control over actions? This project uses electrophysiology recordings and optical fibers implanted in the brain, to register and manipulate brain activity in stressed mice. Behavioral analysis and physiological parameters will also be collected to understand the global impact of stress.

Aims

1-Investigate the neurological impact of stress on specific brain circuits.

2-Determine if stress response can be modulated by stimulating defined regions in the brain.

References

Sousa, N. The dynamics of the stress neuromatrix. Mol Psychiatry. 2016 Mar;21(3):302-12.

Supervisor

Patricia Monteiro and Nuno Sousa

32

Implication of RNA splicing for Machado Joseph Disease

Summary

Machado-Joseph disease (MJD) is a neurodegenerative disorder caused by a polyQ-tract expansion within Ataxin-3 (ATXN3), a deubiquitylating (DUB) enzyme. The precise physiological role of ATXN3 and the molecular mechanism causing selective neurodegeneration remain unknown. We recently found altered polyubiquitylation of several splicing regulatory factors (SRFs) in neuronal cells lacking ATXN3; consistently, these cells showed disturbed splicing profiles. We hypothesize that ATXN3 regulates the turnover of key SRFs through its DUB activity, and that polyQ-expansion may be compromising this interaction, resulting in splicing deregulation of key transcripts, contributing to neurodegeneration. Using biochemical/biophysical and cellular approaches the student will: i) study the interaction of SRFs with ATXN3 and ii) evaluate the regulation of SRFs by ATXN3 DUB activity. We expect to characterize this new ATXN3 biological function and its relevance for MJD, opening new possibilities for rational design of therapeutics.

Aims

-To evaluate interaction of SRFs with non-expanded and mutant ATXN3;
-To evaluate the relevance of ATXN3 DUB activity on the regulation of SRFs turnover.

References

Almeida, B., Fernandes, S., Abreu, I.A. and Macedo-Ribeiro, S. Trinucleotide repeats: a structural perspective, Front Neurol, 4 (2013) 76.

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P.O. Bauer, N. Nukina, The pathogenic mechanisms of polyglutamine diseases and current therapeutic strategies, Journal of neurochemistry, 110 (2009) 1737-1765.

Supervisor

Bruno Almeida and Patrícia Maciel

33

Functional correlates of adult hippocampal cytogenesis: a matter of sex and time?

Summary

Along with the subependymal-olfactory bulb system, the hippocampus is one of the two regions of the adult brain that retains the ability to generate new cells throughout life. Indeed, within the hippocampal dentate gyrus, neural stem cells (NSCs) have the ability to continuously generate new neuronal or astroglial cells, in a process called neurogenesis or astrogliogenesis, respectively.

Understanding how these new cells in the adult hippocampus can reshape brain circuits and affect different behavioral functions is a complex task. This complexity emerges primarily from the difficulty to precisely segregate the function of newborn cells from the preexisting neuron-glia cell network in which they are integrated. Moreover, there is sufficient evidence to support the notion that cytogenesis functional roles are variable according to **(i)** factors that are intrinsic to the studied animals (eg. young adult *vs* old; *female* vs *male),* **(ii)** experimental interference (eg. physiological/basal conditions *vs* disease states or pharmacological interventions) and **(iii)** the time-window of the analysis (eg. newly-formed cells *vs* 6-weeks old, fully integrated new cells).

Hence, to better dissect the functional roles of new hippocampal cells, here we will use the transgenic GFAP-Tk rat model to specifically ablate GFAP-expressing NSCs in the adult mammalian brain. We will then perform a longitudinal characterization of the impact of cytogenesis ablation in different emotional and cognitive behavioral dimensions, addressing the differential role of immature vs mature newborn cells. Furthermore, a comparison analyses betweens male and female animals will be perform to characterize putative sex-specific functional correlates of adult hippocampal cytogenesis

Aims

Induce cytogenesis ablation in GFAP-Tk adult male and female rats

Explore the functional consequences of cytogenesis ablation in different behavioral test paradigms

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Supervisor

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Immunological aging as a trigger for multiple sclerosis

Summary

Multiple Sclerosis (MS) is an autoimmune disorder of the central nervous system mediated by T lymphocytes, and characterized by progressive demyelination, axonal damage and neuronal loss. MS develops in two major forms: the relapsing-remitting (RRMS), characterized by bouts of neurological impairment interleaved with recovery periods, followed by a progressive phase; and the primary progressive (PPMS) with a sustained disability accumulation from onset. PPMS onset tends to occur 10 years later than RRMS (mean 40 vs 29 years). We hypothesize that the development of one or the other MS form depends on inter-individual differences on the T cells aging. In accordance, children with MS revealed signs of premature T cells aging, a process that normally initiates at young adulthood, but that displays great inter-individual differences.

The aim of the project is to clarify how T cells aging impacts on MS and its phenotypes. For this, in blood samples from MS patients, the distinct forms of the disease will be related to thymic output (quantification of recent thymic emigrants by flow-cytometry and of T-lymphocytes receptor excision circles by qPCR) and T-lymphocytes' aging (telomere length determined by flow-FISH).

Aims

To assess how T cells aging impacts on MS and its phenotypes. To do so parameters that determine the degree of T cells aging will be dissected in 4 groups of patients according to their onset age: RRMS and PPMS with onset at <=40 and >40 years.

References

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Supervisor

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35

Exploring the involvement of striatum in the pathology of Machado-Joseph disease: study in a mouse model

Summary

Machado-Joseph disease (MJD) is an autosomal dominant neurodegenerative disorder for which no effective treatment is currently available. MJD is characterized by motor uncoordination and gait ataxia, difficulty with speech and swallowing, spasticity, altered eye movements, double vision, and frequent urination. Some patients have dystonia (sustained muscle contractions that cause twisting of the body and limbs, repetitive movements, abnormal postures, and/or rigidity), others have peripheral neuropathy and loss of muscle strength or symptoms similar to those of Parkinson's disease. The cerebellum and brainstem atrophy is well documented in MJD. Recent studies have shown that the neuropathology of this disease is not limited to cerebellum and brainstem, eventually affecting the integrity of several functional and neurotransmitter systems resulting in severe and widespread neuropathology throughout the brain, including the striatum. We have generated a new transgenic mouse model expressing human ataxin-3 with an expanded CAG tract ubiquitously and at near-endogenous levels – the CMVMJD135. This mouse model mimics the human disorder quite closely at the phenotypic level. The disease symptoms of this model appear gradually in life and progress as the mice age. Motor and gait deficits, loss of muscular strength and other neurological symptoms such as abnormal reflexes and tremors are present. This model also present intranuclear inclusions, as well as neuropathologic affection in key disease regions resembling the human disease such as (i) cellular loss in the pontine and dentate nuclei, in substantia nigra and spinal cord (ii) a reduction of calbindin positive Purkinje cells as well as a reduced thickness of the molecular layer of the cerebellum, (iii) reduced cholinergic neurons in the facial nuclei and spinal cord, (iv) a reduction of TH positive neurons and astrogliosis in the substantia nigra, (v) gross brain atrophy (late in life) and (vi) and alterations in the brain cytokine profile, as was described for MJD patients. Little is known the involvement of striatum in MJD, being the main goal of this lab rotation the study of its involvement in MJD pathology.

Aims

- Perform immunohistochemistry in the striatum to:
    - Quantify astrogliosis, using the GFAP astrocyte marker
    - Evaluate microgliosis using Iba-1 microglia marker
    - Measure the DARPP-32 (dopamine- and cAMP-regulated neuronal phosphoprotein) immunoreactivity
    - Measure the number of ChAt positive cells (cholinergic neurons marker)
    - Verify the presence/absence of ataxin-3 positive aggregates.

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Supervisors

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Exploring Sorting Nexin 27 role in *Mycobacterium avium* infection

Summary

Endocytic dysregulation can affect the ability to mount an appropriate immune response, by impacting on antigen presentation and antigen receptor signaling [1]. Recently, the Sorting nexins (SNXs) emerged as a novel family of highly conserved proteins that facilitate protein trafficking and cell signaling [2,3], thus modulating the presence/abundance of proteins/receptors at the cell surface and also their pathological accumulation/clearance. Reports linking SNXs and endocytic events underlying distinct diseases and pathogen invasion, are growing in number [3]. In fact, distinct studies established a prominent role for SNX3 in the down-modulation of phagocytosis [4] and of SNX27 in immunological-synapses during T cell activation [5]. Specifically, SNX27 has been demonstrated to interact with diacylglycerol kinase z (DGKz), a negative regulator of T cell function and to regulate the Ras-ERK pathway, in T cells that encounter pulsed antigen-presenting cells [5]. Despite this, not much is known about SNX27 role in the immune system, namely on how its function is modulated during infection with a pathogenic agent. Taking advantage of the SNX27+/- mouse model we aim to dissect SNX27 role during infection with *Mycobacterium avium*. For that, SNX27 heterozygous mice (KO mice are not viable) and littermate wild-type controls will be infected with *M. avium* 2447. Animals will then be analysed for several behavioral dimensions: locomotion, emotion and cognition. Behavioral assessment will be performed at 4 and 12 weeks post infection in the following order: elevated plus maze (EPM; anxiety-like behavior), open field (OF; locomotor and exploratory behavior), forced-swim test (FST; depressive-like behavior), working memory water maze (WM; spatial short-term memory), Morris water maze (MWM; spatial reference memory) and spatial reversal (behavioral flexibility). Simultaneously, blood samples will be collected for flow-cytometry analysis of the immune cell population. Tissue samples will also be collected (liver, thymus, spleen, lungs and brain) for CFU quantification and flow-cytometry analysis.

Aims

- Evaluate distinct behavioral dimensions in control and *M. avium* infected wild-type and Snx27+/- mice.
- Quantify CFUs in distinct organs of *M. avium* infected wild-type and Snx27+/- mice.
- Analyze immune cell populations in control and *M. avium* infected wild-type and Snx27+/- mice.

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Supervisors

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Tau function and dysfunction: characterization of a neuronal cell line

Summary

The microtubule-binding protein tau (MAPT) is predominantly expressed in neurons (1). Tau is a multifunctional protein, but its major known biological function is the assembly and stabilization of microtubules, contributing to morphogenesis, cell division, axonal extension and axonal transport (2). Much evidence has been accumulated pointing to the contribution of tau to Alzheimer's disease (AD) pathology either by loss of function (such as stabilization of microtubules) as well as gain of toxic function (aggregation and deposition of neurofibrillary tangles) (3). Although these data provide a better understanding of tau pathogenesis, the disappointing clinical outcomes of therapeutic approaches suggest that continuing efforts towards understanding tau pathology in AD as well as unravel the physiological functions of tau are needed. Thus, this project aims to focus in tau's function and dysfunction using a human neuronal model. This will provide an unique opportunity to improve our knowledge of the biological pathways tau belongs to in a human environment and to a better understanding of the AD-disease mechanisms, contributing to improved therapeutical strategies.

Aims

1 – To characterize the phenotype of neuronal cell lines overexpressing Wild type and pathogenic tau

2 – To study the effects of pathogenic tau on cell morphology, cytoskeleton, proliferation, migration and differentiation

3 – To analyze the relevance of the findings for AD in a mouse model for the disease.

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Supervisors

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