Postdoctoral Fellowship under the Marie S. Curie Actions Cofund project "Opening Sphere UAB-CEI to Postdoctoral Fellows (P-Sphere)" Gran Agreement 665919.

Department or Institution involved

Dissecting neuronal susceptibility to mitochondrial disease

Topic description

Mitochondria generate most of the energy cells require to function. Deficits in the mitochondrial energy-generating machinery affect 1:5,000 children and cause progressive, debilitating, and usually fatal pathologies collectively known as primary mitochondrial disease. To date, there is no cure for mitochondrial disease and existing treatments are highly ineffective and mostly palliative. High-energy-requiring cells, such as neurons, are especially affected in mitochondrial disease. However, not all neuronal populations are equally affected. Furthermore, the molecular determinants of neuronal vulnerability to mitochondrial disease have not been adequately elucidated, representing a challenge for the development of efficient treatments for these pathologies.

Our previous work involved the generation and characterization of a mouse model lacking Ndufs4, a subunit of the mitochondrial complex I involved in the assembly and stability of the complex. Humans harbouring mutations in NDUFS4 develop a severe form of MD (Leigh Syndrome) and die at an early age, commonly presenting brain lesions, hypotonia and respiratory deficits. Mice lacking this protein (Ndufs4KO) recapitulate the human symptoms and are an excellent correlate of the human pathology (Quintana, Kruse et al. 2010) and identified that mTOR (Johnson, Yanos et al. 2013) and JNK pathways (Liu, Zhang et al. 2015) play a key role in the disease.

Our lab has identified that the brainstem vestibular nucleus (VN) is severely affected in Ndufs4KO. A subset of vestibular neurons show enhanced susceptibility to Ndufs4 deficiency (Quintana, Kruse et al. 2010). Furthermore, conditional Ndufs4 ablation restricted to the VN causes a pathology similar to global Ndufs4KO mice. Conversely, viral-mediated of Ndufs4 re-expression in the VN is sufficient to ameliorate the pathology and to extend the lifespan of Ndufs4KO mice by rescuing the breathing alterations (Quintana, Zanella et al. 2012). However, the role of the VN in the control of autonomic functions has been described to an anatomical level, but the nature and the circuitry involved in these responses and its contribution to MD is unknown.

Therefore, we are interested in defining the molecular identity and connectome of the VN population(s) involved in the pathological signs of mitochondrial disease. To this end, interested candidates will combine molecular biology, mouse genetics, in vivo electrophysiology and optogenetic approaches to characterize the molecular, physiological and functional signatures of vestibular neurons in the context of mitochondrial disease.

- Johnson, S. C., M. E. Yanos, E. B. Kayser, A. Quintana, M. Sangesland, A. Castanza, L. Uhde, J. Hui, V. Z. Wall, A. Gagnidze, K. Oh, B. M. Wasko, F. J. Ramos, R. D. Palmiter, P. S. Rabinovitch, P. G. Morgan, M. M. Sedensky and M. Kaeberlein (2013). "mTOR inhibition alleviates mitochondrial disease in a mouse model of Leigh syndrome." Science 342(6165): 1524-1528.
- Liu, L., K. Zhang, H. Sandoval, S. Yamamoto, M. Jaiswal, E. Sanz, Z. Li, J. Hui, B. H. Graham, A. Quintana and H. J. Bellen (2015). "Glial lipid droplets and ROS induced by mitochondrial defects promote neurodegeneration." Cell 160(1-2): 177-190.
- Quintana, A., S. E. Kruse, R. P. Kapur, E. Sanz and R. D. Palmiter (2010). "Complex I deficiency due to loss of Ndufs4 in the brain results in progressive encephalopathy resembling Leigh syndrome." Proc Natl Acad Sci U S A 107(24): 10996-11001.
- Quintana, A., S. Zanella, H. Koch, S. E. Kruse, D. Lee, J. M. Ramirez and R. D. Palmiter (2012). "Fatal breathing dysfunction in a mouse model of Leigh syndrome." J Clin Invest 122(7): 2359-2368.

Project supervisor & hosting group

Dr. Albert Quintana is a Ramón y Cajal investigator and group leader at the Universitat Autònoma de Barcelona. He obtained his PhD in 2007 (UAB, Spain) and performed post-doctoral research in Dr. Richard Palmiter lab (HHMI-UW, Seattle, USA). In 2013 he became an independent investigator (Seattle Children's Research Institute) and in 2015 he was hired by the Universitat Autonoma de Barcelona.

The hosting group is widely recognized for its activities in the area of neuropathology in mitochondrial disease, with special emphasis on molecular biology, biochemistry and physiology. The lab focuses on the use of mouse genetics to characterize molecular alterations in neurons in the context of mitochondrial disease.

More information can be found at: www.quintanalab.org

The main relevant projects associated with data science are:

- NEUROMITO: Elucidating neuronal susceptibility to mitochondrial disease. Funding agency: European Union (ERC-2014-StG 638106). Dates: From 2015 to 2020.
- Caracterización de las alteraciones moleculares en poblaciones neuronales susceptibles en un modelo de enfermedad mitocondrial. Funding Agency: Ministerio de Economía y Competitividad (SAF2014-57981-P). Dates: From 2015 to 2018

Planned secondments

We have relevant collaborations with external organizations that can be considered for secondments. The expected duration of the secondments will be 2 months.

- Dr. Ali Guler, University of Virginia, USA. The aim of this secondment will be to gain knowledge in In-vivo Electrophysiology and Optogenetics.
- Dr. Richard Palmiter, Howard Hughes Medical Institute – University of Washington, Seattle. USA. The aim of this secondment will be to gain knowledge in molecular biology, development of new tools and mouse genetics.

Candidate's profile

A PhD in Biology or equivalent life sciences field.

Specific abilities and skills:

- Ample experience in neuroscience, molecular biology, animal handling, mouse models (animal training certification required) and biochemistry.
- Experience in MATLAB programming, electrophysiology and tissue culture will be valued.

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