May 16th, 1:45 PM

Poly (GR) in C9ORF72-related ALS/FTD Compromises Mitochondrial Function and Increases Oxidative Stress and DNA Damage in iPSC-derived Motor Neurons

Rodrigo Lopez-Gonzalez
University of Massachusetts Medical School

Let us know how access to this document benefits you.
Follow this and additional works at: https://escholarship.umassmed.edu/cts_retreat

Part of the Neuroscience and Neurobiology Commons, and the Translational Medical Research Commons

Repository Citation

Creative Commons License
This work is licensed under a Creative Commons Attribution-Noncommercial-Share Alike 3.0 License.
This material is brought to you by eScholarship@UMMS. It has been accepted for inclusion in UMass Center for Clinical and Translational Science Research Retreat by an authorized administrator of eScholarship@UMMS. For more information, please contact Lisa.Palmer@umassmed.edu.
POLY (GR) IN C9ORF72-RELATED ALS/FTD COMPROMISES MITOCHONDRIAL FUNCTION AND INCREASES OXIDATIVE STRESS AND DNA DAMAGE IN IPSC- DERIVED MOTOR NEURONS

Rodrigo Lopez-Gonzalez, PhD¹, Yubing Lu, PhD¹, Tania F. Gendron, PhD², Anna Karydas³, Helene Tran, PhD¹, Dejun Yang, PhD¹, Leonard Petrucelli, PhD², Bruce L. Miller, MD³, Sandra Almeida, PhD¹, and Fen-Biao Gao PhD¹

¹Department of Neurology, University of Massachusetts Medical School; ²Department of Neuroscience, Mayo Clinic Florida, Jacksonville, FL; ³Memory and Aging Center, Department of Neurology, University of California, San Francisco, San Francisco, CA

GGGGCC repeat expansions in C9ORF72 are the most common genetic cause of both ALS and FTD. To uncover underlying pathogenic mechanisms, we found that DNA damage was greater, in an age dependent manner, in motor neurons differentiated from iPSCs of multiple C9ORF72 patients than control neurons. Ectopic expression of the dipeptide repeat (DPR) protein (GR)80 in iPSC-derived control neurons increased DNA damage, suggesting poly(GR) contributes to DNA damage in aged C9ORF72 neurons. Oxidative stress was also increased in C9ORF72 neurons in an age-dependent manner. Pharmacological or genetic reduction of oxidative stress partially rescued DNA damage in C9ORF72 neurons and control neurons expressing (GR)80 or (GR)80-induced toxicity in flies. Moreover, interactome analysis revealed that (GR)80 preferentially bound to mitochondrial ribosomal proteins and caused mitochondrial dysfunction. Thus, poly(GR) in C9ORF72 neurons compromises mitochondrial function and causes DNA damage in part by increasing oxidative stress, revealing another pathogenic mechanism in C9ORF72-related ALS and FTD.

Contact:
Rodrigo Lopez Gonzalez, PhD
Postdoctoral Associate
Department of Neurology
University of Massachusetts Medical School
Rodrigo.LopezGonzalez@umassmed.edu