Barbara Carletti, J Cell Sci Ther 2012, 3:7
http://dx.doi.org/10.4172/2157-7013.S1.002

OMICS Group Conferences
Accelerating Scientific Discovery

International Conference on
Emerging Cell Therapies

October 1-3, 2012 DoubleTree by Hilton Chicago-North Shore, USA

A friedreich's ataxia neuronal cell model with evidence of oxidative stress-mediated neurodegeneration

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Friedreich's ataxia (FRDA) is caused by severely reduced levels of frataxin as a result of a large GAA triplet-repeat expansion within the first intron of the frataxin gene. The prominent feature of this pathology is the neurodegeneration interesting both central and peripheral nervous systems. A distal length-related axonal degeneration affects upper motor neurons of the corticospinal tract, the posterior columns of the spinal cord, the spinocerebellar tract and the large sensory fibers of the peripheral nerves. To date, there is still no known pharmacological treatment that cures, or even slows down, FRDA neuropathology. Indeed, the study of the selective vulnerability of specific neurons to frataxin deficiency is make it difficult by the scarce accessibility of the nervous tissue and by the lack of an appropriate neuronal cell model which reproduces the pathophysiology associated to FRDA.

We developed for the first time an in vitro system of FRDA neuronal degeneration by using the NSC34 motoneuronal cell line in which frataxin deficiency was obtained via shRNA gene silencing with a reduction of the protein ranging from 30% to 60% of the normal level. Frataxin-silenced NSC34 cells show a specific inhibition of mitochondrial Complex I activity and undergo to oxidative stress evidenced by a dramatic glutathione unbalance. In addition, FRDA cells show a decrease of cell proliferation rate. Interestingly, the in vivo treatment with the permeable form of glutathione (EE-GSH) cause a significant induction of cell proliferation and the in vitro re-activation of Complex I.

Our neuronal cell model have the potential to provide an experimentally accessible cell population to allow a more detailed examination, not only of nervous tissue specific FRDA pathophysiology, but also of oxidative stress-mediated neurodegeneration. In addition, it suggests glutathione as possible target for new therapeutic treatments.

Biography

Barbara Carletti began her scientific career studying the development of neural progenitor cells by using the cerebellum as model system. She joined Dr. Ferdinando Rossi's research group at the University of Turin in 2000 after getting her Master's Degree in Biology at the University of Siena and she was enrolled in the PhD program in Neuroscience. At the beginning of 2007 she left Dr. Rossi's Department and joined the laboratory of Dr Carol Ann Mason at Columbia University, New York. She is currently working as junior research biologist at the "Bambino Gesù" Children's Hospital in Rome. She has published 12 papers in peer-reviewed journals.

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