Australian Synchrotron
USER MEETING 2014
20 – 21 November
National Centre for Synchrotron Science

Contribution ID : **57** Type : **Oral**

Zinc complex rescues subcellular zinc and calcium mislocalisation in batten disease

Thursday, 20 November 2014 14:20 (20)

A hallmark of neurodegeneration is a failure of homeostatic mechanisms controlling the concentration and distribution of biometals. A major roadblock to understanding the impact of altered biometal homeostasis in neurodegenerative disease is the lack of specific and sensitive techniques capable of providing quantitative subcellular information on biometals in situ. Advances in X-ray fluorescence detectors provide an opportunity to rapidly measure biometal content at subcellular resolution in cells using X-ray Fluorescence Microscopy (XFM). We investigated subcellular biometal homeostasis in a cerebellar cell line from a natural mouse model of a childhood neurodegenerative disorder, the CLN6 form of Batten Disease. Despite no global cell concentration changes, XFM revealed significant subcellular mislocalisation of zinc and calcium in cerebellar Cln6nclf cells. XFM revealed that nuclear-to-cytoplasmic trafficking of zinc was severely perturbed in diseased cells and the subcellular distribution of calcium was drastically altered in Cln6nclf cells. Subtle differences in the zinc XANES spectra of control and Cln6nclf cells suggested that impaired zinc homeostasis may be associated with an altered ligand set in Cln6nclf cells. Importantly, a zinc-complex, ZnII(atsm), restored the nuclear-to-cytoplasmic zinc ratios in Cln6nclf cells via nuclear zinc delivery, and restored the relationship between subcellular zinc and calcium levels to that observed in healthy control cells. ZnII(atsm) treatment also resulted in a reduction in the number of calcium-rich puncta observed in Cln6nclf cells. This study highlights the complementarities of bulk and single cell analysis of metal content for understanding disease states.

Keywords or phrases (comma separated)

Zinc, XFM, neurodegeneration, calcium, XANES, biometal homeostasis, CLN6

Summary

Primary author(s) : Dr GRUBMAN, Alexandra (University of Melbourne)

Co-author(s) : Prof. WHITE, Anthony (University of Melbourne); Dr LIDDELL, Jeffrey (University of Melbourne); Dr DE JONGE, Martin (Australian Synchrotron); Dr DONNELLY, Paul (University of Melbourne); Dr JAMES, Simon (Australian Synchrotron)

Presenter(s) : Prof. WHITE, Anthony (University of Melbourne)

Session Classification : Biological Systems

Track Classification : Biological Systems