



THE HONG KONG UNIVERSITY OF SCIENCE & TECHNOLOGY
Division of Life Science

LIFS Seminar Series

When the ATM is broken cash withdrawals fail
(The role of ATM kinase in responding to cellular ATP demand through modulating mitochondrial bioenergetics)

by

Dr. Kim Heiman CHOW
HKUST

Abstract:

Ataxia telangiectasia (AT) is a rare (3/million) recessively inherited disorder resulting in debilitating multi-system disease with severe neurological decline for which there is no therapy; nor does the field understand the ties between ATM loss and the underlying cause of pronounced vulnerability observed in the Purkinje cells. Here, analyses with the human A-T cerebella expression array and symptoms dataset revealed that cerebellar atrophy and ataxia, but not other clinical symptoms of A-T, are highly associated with metabolic defects resulting from dysfunctional TCA cycle and oxidative phosphorylation (OXPHOS). The resulting ATM-deficient neurons showed impaired capacities to enhance ATP production in response to increased energy demands upon sustained neuronal activities. Mechanistically, systems analyses using the array dataset indicated that loss of activity of nuclear respiratory factor-1 (NRF1) is the most likely link underlying the global changes in gene expression observed in A-T. NRF1 is a classic trans-activator of nuclear-encoded respiratory genes. At molecular level, our data indicated that NRF1 is highly enriched in the Purkinje cells, and is a novel target of ATM. Phosphorylation at T259 residue by ATM enhanced its homo-dimerization and subsequent nuclear localization. This process is mediated when ATM is activated by mitochondrial oxidative stress, at times during ATP insufficiencies. Taken together, our data indicated that ATM facilitates the mitochondrial-nuclear communication in response to surges in cellular energy demand. A failure to cope with such changes therefore leads to Purkinje cell death and childhood-onset of ataxia.

Date : **1 December 2017 (Friday)**
Time : **4:00 p.m.**
Venue : **Lee Wing Tat Lecture Theater D (LT-D)**

(Host faculty: Prof Karl Herrup)

All are Welcome!!