BioSys-PhD
Biological Systems - Functional & Integrative Genomics

BioISI
Biosystems and Integrative Sciences Institute

BioSys/BioISI Research Seminar

CAG repeat translational fidelity as a therapeutic avenue for treating polyglutamine disease

Aaron Voigt, PhD
Department of Neurology, Aachen University Medical Centre

Polyglutamine (polyQ) diseases like Huntington's disease (HD) and several Spinocerebellar ataxias have one commonality, an expanded CAG stretch within the coding region, translated in a glutamine tract of various lengths in disease causing proteins. The polyQ stretch is causative for and correlated with disease. The longer the stretch, the more severe is the disease. Although of monogenetic nature and easy to diagnose even before disease onset, no therapy is available to interfere with the neuronal decline in polyQ diseased patients.

We identified TRMT2A as a suppressor of polyQ-induced toxicity and aggregation in an unbiased Drosophila screen. The same findings were observed in yeast, human HEK293T cells and fibroblast derived from patients with Huntington's disease. In these cells, siRNA mediated silencing of TRMT2A ameliorated toxicity and aggregation of polyQ proteins.

TRMT2A catalyses the methylation of tRNAs at a specific position, conserved from bacteria to humans. Loss of TRMT2A causes a lack of this methylation, but apart of that, does not result in any obvious phenotypes in yeast, flies and mice. We show that a lack of the TRMT2A dependent methylation reduces the fidelity of tRNAs towards their particular amino acid. Thus, loss of TRMT2A might indirectly cause changes within the polyQ stretch by amino acid replacement. The resulting interrupted polyQ tract is expected to cause reduced toxicity and aggregation.

We conclude that silencing of TRMT2A (function) might be a promising approach for future therapies of polyQ diseases.

Date: 17th January 2017 – 10h00

Faculdade de Ciências da UL, Lisboa (Portugal), FFCUL Auditorium

PD-F FCT PhD PROGRAMMES

FCT Fundação para a Ciência e a Tecnologia
MINISTÉRIO DA CIÊNCIA, TECNOLOGIA E ENSINO SUPERIOR

U LISBOA | UNIVERSIDADE DE LISBOA

Ciências ULisboa