MBG FOCUS TALK

hosted by Erik Østergaard Jensen

MBG Focus Talks in Molecular Biology

Wednesday August 5, 2020, at 9:15 - 10:00

The science park conference room (3130-303)

Professor Daan van Aalten

Division of gene Regulation and Expression, University of Dundee

The O-GlcNAc modification and its role in neurodevelopmental delay

Protein O-GlcNAcylation is a reversible posttranslational modification of Ser/Thr on nucleocytoplasmic proteins in metazoa. This modification is essential for life at the single cell level and regulates a range of cellular processes such as metabolism, transcription, translation and signalling pathways. Defects in protein O-GlcNAcylation have been linked to diabetes, cancer and neurodegenerative disease. However, the link between O-GlcNAcylation of specific proteins and these processes/diseases remains largely unexplored. Deletion of the O-GlcNAc transferase (OGT) or O-GlcNAc hydrolase (OGA) genes in invertebrate/vertebrate models gives rise to lethality. Using the remarkable developmental phenotypes of O-GlcNAc deficient Drosophila as a starting point, my lab is focused on discovering the O-GlcNAc proteins linked to these phenotypes, and the cellular processes involved, using a combination of chemical biology, structural biology, biochemistry and genetics. We have been the first to describe the structures and mechanisms of the OGA and OGT enzymes. We have then exploited this detailed structural knowledge to design potent inhibitors, and applied these to study the effect of modulating cellular O-GlcNAc levels and the effects on specific signalling pathways. Currently we are developing novel tools for the enrichment and MS/MS identification of O-GlcNAc proteins from Drosophila embryos and are inducing hypo-O-GlcNAcylation by means of CRISPR/Cas9 gene editing technology and the delivery of specific OGT inhibitors to ultimately allow us to study the mechanisms behind individual O-GlcNAc sites. In the last few years we have discovered families with X-linked intellectual disability that have inherited missense mutations in OGT. A large part of the lecture will be devoted to recent unpublished results describing our progress towards understanding the links between the molecular and phenotypic consequences of these mutations.

Bio:
Daan van Aalten: BSc Chemistry 1994 (Nijmegen, NL), PhD Biochemistry 1997 (Leeds, UK), Postdoc 1997-1999 (Cold Spring Harbor, NY, US), Postdoc 1999 (University of Oulu, FI), Lecturer (1999), Reader (2004), Full Professor (2006-) at School of Life Sciences, University of Dundee. Recipient of EMBO YIP (2001), Lister Prize (2006), Wellcome Trust Career Development Award (2000), Senior Fellowships (2004 & 2009) and Investigator Award (2016). >200 peer reviewed papers (H-factor = 59). Research interests: molecular and biological mechanisms of O-GlcNAc signalling, biogenesis of the fungal cell wall and associated target discovery/validation.