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20/03/2014

THURSDAY **start 14.00**

Seminar room 1.32, pavilion A11
University campus Bohunice

CEITEC STRUCTURAL BIOLOGY SEMINAR SERIES

You are cordially invited to the lecture

„RNA 3' end modifications in cancer development“

delivered by

Chris J. Norbury
University of Oxford

Abstract:

Our work is currently focused on post-transcriptional aspects of gene regulation, and specifically how these differ between cancer cells and their normal counterparts.

The DNA polymerase β superfamily encompasses a diverse group of nucleotidyl transferases that share a common catalytic sequence motif. We previously detected the addition of non-templated UMP residues to the 3' ends of cytoplasmic, polyadenylated mRNAs in the fission yeast Schizosaccharomyces pombe, and showed was carried out by the RNA nucleotidyl transferase Cid1. Cid1-mediated mRNA uridylation acts independently from deadenylation to stimulate decapping and hence turnover of a wide variety of mRNAs. In human cells the Cid1 orthologue ZCCHC11 acts in a similar way to target replication-dependent histone mRNAs for decapping and degradation following inhibition of DNA synthesis. Remarkably, ZCCHC11 is also responsible for the modification of tumour suppressor micro-RNA precursors and mature micro-RNAs. Inhibition of ZCCHC11 expression in cancer cells has been shown to block some of the aspects of the cancer phenotype in vivo, and recent data suggest that ZCCHC11 over-expression predicts disease progression in breast cancer. Furthermore, the 3´-5´ exonuclease Dis3L2 was recently shown by others to be responsible for the degradation of uridylated pre-microRNAs and mRNAs in mammals and S. pombe, respectively. Human germline Dis3L2 mutations are the underlying cause of the foetal overgrowth syndrome Perlman syndrome, and predispose to the development of Wilm's tumour. Together, these findings suggest that targeting the ZCCHC11 uridylation pathway may be of therapeutic value in a variety of cancers.

We have recently studied the relationship between the structure of Cid1 and its biochemical activity. Although Cid1 lacks a canonical RNA recognition motif, we found that it binds RNA substrates in a sequence-independent manner, but with high affinity, by a novel mechanism. The architecture of the active site, revealed by crystal structures of Cid1 in two Apo conformers and in complex with UTP, identifies a histidine residue (His336) crucial for the UTP selectivity of the enzyme, and conserved in ZCCHC11. Remarkably, mutation of His336 to alanine converted Cid1 from a uridyl transferase to a poly(A) polymerase. These studies will guide further investigation of ZCCHC11 and may make possible the design of selective small molecule inhibitors.

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