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in kemijsko tehnologijo

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VABILO NA PREDAVANJE V OKVIRU DOKTORSKEGA ŠTUDIJA KEMIJSKE ZNANOSTI / INVITATION TO THE LECTURE WITHIN DOCTORAL PROGRAMME IN CHEMICAL SCIENCES

Prof. Erik Storkebaum

Radboud University,
Nijmegen, Netherlands

z naslovom / title:

tRNA sequestration by mutant tRNA synthetases triggers peripheral neuropathy

v sredo, 13. 3. 2024 ob 15. uri /
on Wednesday, 13. 3. 2024 at 15.00
v predavalnici 1 v 1. nadstropju Fakultete za kemijo in kemijsko tehnologijo, Večna pot 113 **/ in lecture room 1,** 1st floor at the Faculty of Chemistry and Chemical Technology, Večna pot 113

Vljudno vabljeni! / Kindly invited!

Abstract:

mRNA translation by the ribosome involves decoding of mRNA triplet codons by tRNAs charged with the correct amino acid. Aminoacyl-tRNA synthetases mediate tRNA charging. For efficient mRNA translation, the cellular tRNA pool needs to be aligned with the mRNA codon demand. Heterozygous mutations in 7 cytoplasmic tRNA synthetases cause peripheral neuropathy. We recently reported that peripheral neuropathy associated with mutations in glycyl-tRNA synthetase (GlyRS) results in sequestration of tRNAGly by the mutant GlyRS, thus depleting the cellular tRNAGly pool under a critical threshold. This results in insufficient tRNAGly substrate for wild type GlyRS (derived from the wild type GARS allele in heterozygous patients), insufficient glycyl-tRNAGly production, and ribosome stalling on glycine codons. Ribosome stalling triggers GCN2-mediated activation of the integrated stress response (ISR) selectively in affected motor and sensory neurons. Consistent with this mechanism, transgenic tRNAGly overexpression rescues both inhibition of mRNA translation and peripheral neuropathy phenotypes and prevents ISR activation in Drosophila and mouse models of GlyRS-associated peripheral neuropathy. Therefore, elevating tRNAGly levels may constitute a novel therapeutic approach for GlyRS-associated peripheral neuropathy. Ongoing work revealed that tRNA sequestration also underlies peripheral neuropathy associated with mutations in tyrosyl-tRNA synthetase. Thus, identifying the molecular root cause of these forms of CMT uncovered elevating tRNA levels as a novel therapeutic approach.