Katedry biochémie a genetiky PriF UK
a občianske združenie *NATURA*

Vás pozývajú na 131. prednášku v rámci Kuželových seminárov:

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TRNT1 AND tRNA MATURATION: UNRAVELING THE MOLECULAR PATHOPHYSIOLOGY OF SIFD

ktorá sa uskutoční **30. októbra 2024** (streda) o **13:30**
v miestnosti **CH1-222** Prírodovedeckej fakulty UK

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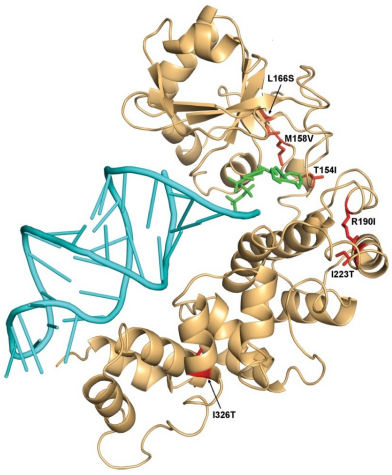
Martin Holcik is a Professor and Chair in the Department of Health Sciences at Carleton University (since September 2017). Prior to this, he was a Senior Scientist at the Apoptosis Research Center of the Children's Hospital of Eastern Ontario Research Institute, Full Professor in the Department of Pediatrics at the University of Ottawa, and Director of the Molecular Biomedicine Program of the Children's Hospital of Eastern Ontario Research Institute. Dr. Holcik received his B.Sc. and M.Sc. from the Comenius University in Bratislava, followed by Ph.D. from Carleton University (Ottawa, Canada). Dr. Holcik is a recipient of numerous awards including the Canadian Institutes of Health Research New Investigator Award (2001), Premier's Research Excellence Award (2004), Faculty of Medicine Young Professor Award (2007), the University of Ottawa Young Researcher Award (2007), and the CHEO Research Institute Award of Excellence (2009), and The Faculty Graduate Mentoring Award (2022). Dr. Holcik is interested in the investigation of the regulation of protein synthesis, with specific emphasis on selective mRNA translation during pathophysiological cellular states such as cellular stress, apoptosis and cancer, or in connection with rare genetic disorders. Dr. Holcik has mentored numerous students, postdoctoral fellows and research associates with whom he has written 11 book chapters, and over 100 articles in academic journals. He has been an invited speaker and organizer of many international conferences and serves on the editorial board of several journals.



Synopsis of the lecture: In this lecture, we will explore the critical role of tRNA Nucleotidyl Transferase 1 (TRNT1) in cellular function and its implications in human disease. TRNT1 is an essential enzyme responsible for adding the CCA trinucleotide to the 3' end of both nuclear and mitochondrial tRNAs, a crucial step in tRNA maturation. Mutations in TRNT1 lead to a multisystemic disorder known as SIFD (sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay). I will discuss how partial loss-of-function mutations in TRNT1 result in a clinically heterogeneous disease with varying severity and symptomatology. Our research has revealed that TRNT1 deficiency is associated with increased sensitivity to oxidative stress, enhanced tRNA cleavage, and alterations in protein translation. Furthermore, we will explore the effects of TRNT1 deficiency on immune cell function, particularly in macrophages, and discuss potential therapeutic approaches for SIFD. This lecture will provide insights into the molecular pathophysiology of SIFD and highlight the broader implications of tRNA metabolism in human health and disease.

Selected publications:

1. Chakraborty PK, Schmitz-Abe K, Kennedy EK, Mamady H, Naas T, Durie D, Campagna DR, Lau A, Sendamarai AK, Wiseman DH, May A, Jolles S, Connor P, Powell C, Heeney MM, Giardina PJ, Klaassen RJ, Kannengiesser C, Thuret I, Thompson AA, Marques L, Hughes S, Bonney DK, Bottomley SS, Wynn RF, Laxer RM, Minniti CP, Moppett J, Bordon V, Geraghty M, Joyce PB, Markianos K, Rudner AD, **Holcik M**, Fleming MD. (2014). Mutations in TRNT1 cause congenital sideroblastic anemia with immunodeficiency, fevers, and developmental delay (SIFD). Blood 124(18):2867-71.
2. Liwak-Muir U, Mamady H, Naas T, Wylie Q, McBride S, Lines M, Michaud J, Baird SD, Chakraborty PK, **Holcik M**. (2016). Impaired activity of CCA-adding enzyme TRNT1 impacts OXPHOS complexes and cellular respiration in SIFD patient-derived fibroblasts. Orphanet J Rare Dis. 11(1):79
3. Slade A, Kattini R, Campbell C, **Holcik M**. (2020). Diseases associated with defects in tRNA CCA addition. Int J Mol Sci. 21(11):3780
4. Fatica T, Naas T, Liwak U, Slaa H, Souaid M, Frangione B, Kattini R, Gaudreau-Lapierre A, Trinkle-Mulcahy L, Chakraborty P, **Holcik M**. (2023) TRNT-1 deficiency Is associated with loss of tRNA integrity and imbalance of distinct proteins. Genes 14(5):1043