Topic

Doctoral study program: Molecular medicine

Research area: Cancer biology, Bio-omics

Supervisor: Mgr. Václav Šeda, Ph.D.

Co-supervisor: Assoc. Prof. Marek Mráz, MSc., M.D., Ph.D.

Topic title: FoxO transcription factors in lymphoproliferative diseases

Annotation:

The goal of this project is to clarify the role of FoxO transcription factors in pathogenesis of lymphoproliferative diseases, with main focus on their contribution to chronic lymphocytic leukemia (CLL) adaptation to targeted therapy. Based on previous studies, FoxO transcription factors were considered as tumor supressors, since their inactivation or deletion is critial pathophysiological process in various cancers, including hematooncological diseases (Xie *et al.*, Blood, 2012). Contrarily, recent data suggest that, under certain conditions, FoxO1 activity can also promote cancerogenesis in lymphomas (Jang *et al.*, JCI, 2022; Kabrani *et al.*, Blood, 2018; Roberto *et al.*, Immunity, 2021). Moreover, in CLL, transcriptional activity of FoxO1 provides adaptational mechanism to BCR inhibitors by inducing IGF1R and GAB1, with both being necessary for sustaining compensatory pro-survival MAPK and Akt signalling, respectively (Scheffold *et al.*, Blood; Seda *et al.*, Blood, 2021). Unpublished data indicate even more profound role of FoxO1 in regulating BCR signalling, which will be further investigated in the course of this project. PhD student will be using technics such as molecular cloning, genome editing (CRISPR), RNA sequencing, use of primary samples, functional studies with various *in vitro* and *in vivo* models. The research is also relevant for pre-clinical development of novel drugs and their combinations.

Recommended literature:

Seda et al…. Mraz FoxO1-GAB1 Axis Regulates Homing Capacity and Tonic AKT Activity in Chronic Lymphocytic Leukemia. Blood 2021 March (epub).
https://pubmed.ncbi.nlm.nih.gov/33786575/

Seda V, Mraz M. B-cell receptor signalling and its crosstalk with other pathways in normal and malignant cells. Eur J Haematol. 2015 Mar;94(3):193-205. doi: 10.1111/ejh.12427. Epub 2014 Sep 13. PMID: 25080849 Review.

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Funding:

Part-time salary (min. 0,5 FTE) on AZV/NPO grants + national scholarship (equals approx. half-time salary)

Requirements on candidates:

- Motivated smart people that have the "drive" to work independently, but also willing to learn from other people in the lab and collaborate.

- Candidates should have a master's degree in Molecular biology, Biochemistry, or similar field and have deep interest in molecular biology and cancer cell biology.

Keywords: CLL, B cell malignancies, BCR signalling, FoxO1, targeted therapy

Information on the supervisor:

11 years of experience in chronic lymphocytic leukemia research; H-index 10 (citations at WOS >300;); patent: 1; Supervisor of 1 diploma thesis; Co-supervisor of 3 diploma thesis; Co-supervisor of 1 bachelor thesis. Internship at Centre Esther Koplowitz in Subero lab, Spain. Genome Engineering: CRISPR/ Cas course at European Molecular Biology Laboratory (EMBL), Germany. Holder of Certificate of professional competence to design experiments and experimental projects for work with animals. Reviewer in scientific journals: Blood Cancer Journal, Frontiers in Oncology. Award for the best presentation Young Investigator meeting, International workshop on CLL (iwCLL), Poland. Award for the best publication published in impacted journal, Purkyně foundation. Award for best publication, League against cancer. https://is.muni.cz/auth/osoba/323515

Information on the co-supervisor:

H-index 22 (citations at WOS > 1600, 61 publications), currently principal investigator of 4 fundings (AZV, ERC, GAMU, NPÚ), international collaborations: University of Southampton, UCSD, Mayo Clinic, Dana-Farber Cancer Institute, EMBL, University of Turin (student internship available), member of EHA Comitte, reviewer in scientific journals: Blood, Leukemia, Leuk Lymphoma, Leukemia Research. https://is.muni.cz/auth/osoba/101627

More information about the research group: http://mrazlab.ceitec.cz/

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